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A.M.A. ARCHIVES OF NEUROLOGY & PSYCHIATRY

SECTION ON NEUROLOGY

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Richard W. Naef

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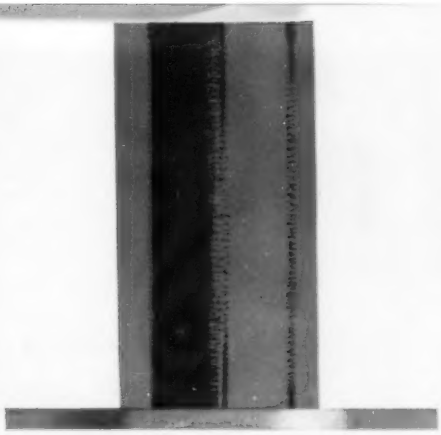

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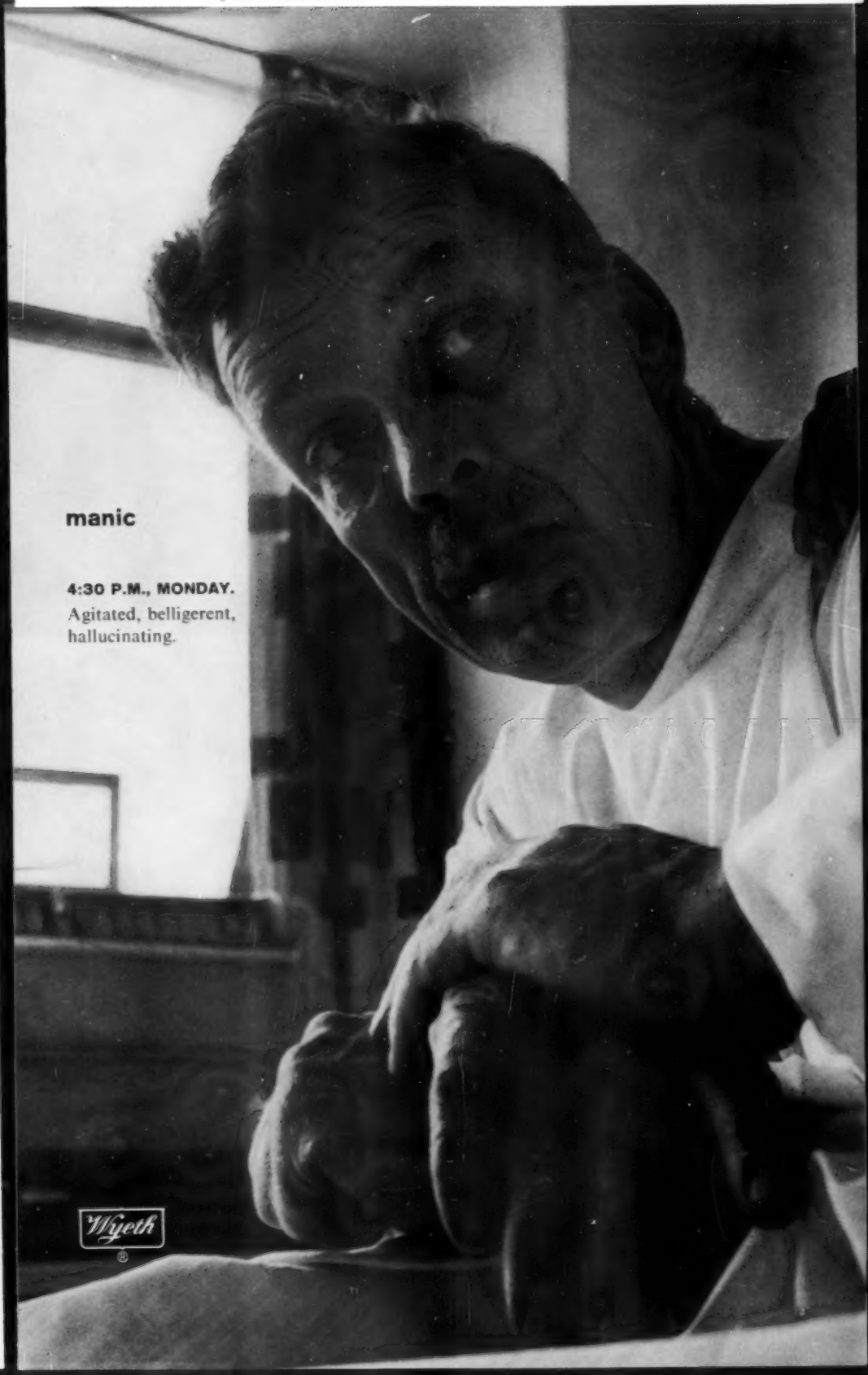
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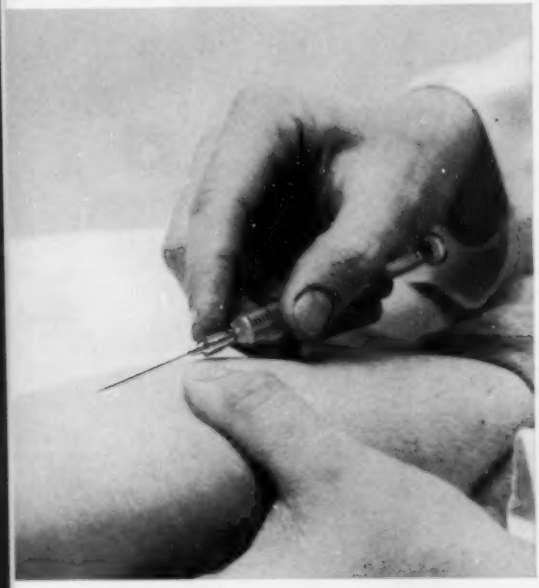

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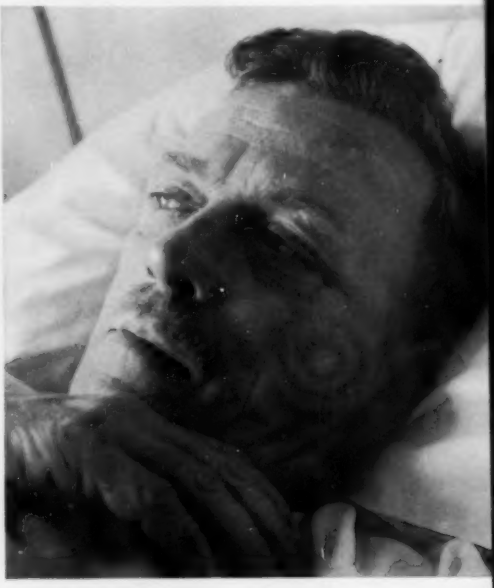
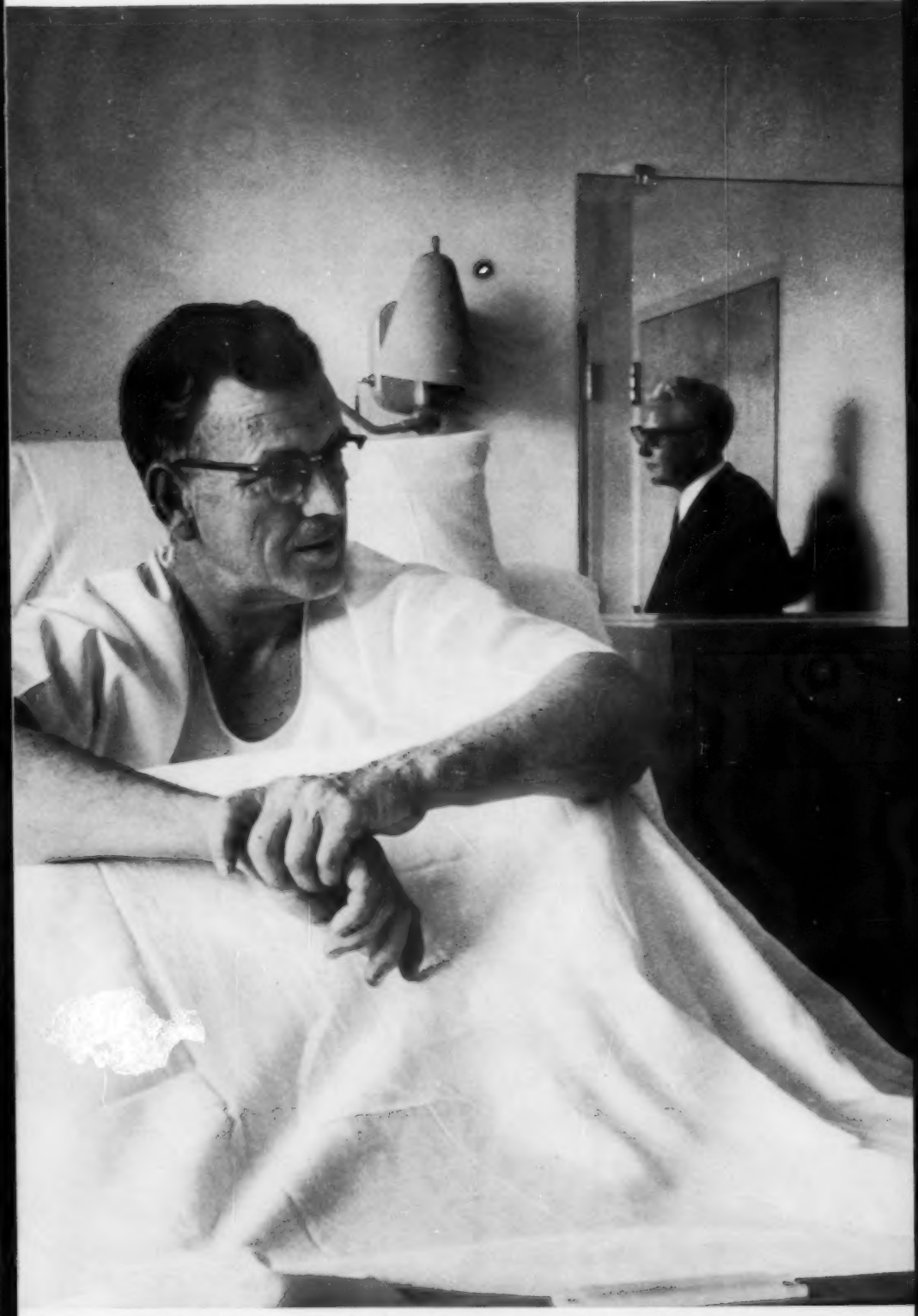


7:30 A.M., TUESDAY. Refreshed but some agitation remains. SPARINE I.V.



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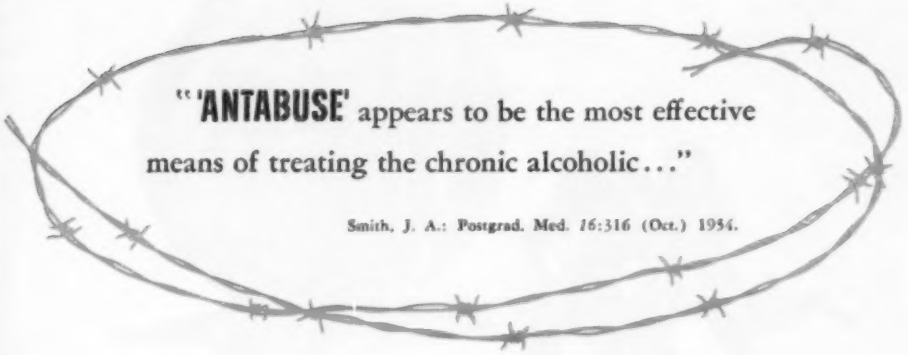

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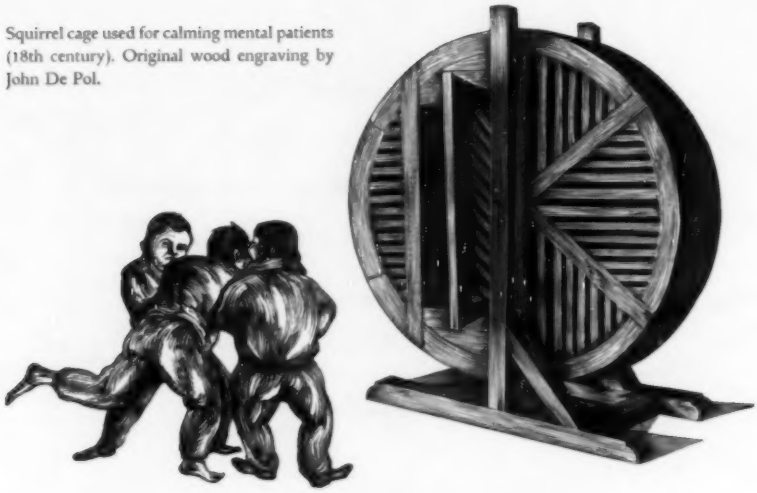

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(hospitalized patients—all types)

by disease

DIAGNOSIS	NO. OF PATIENTS	NO. IMPROVED
SCHIZOPHRENIA		
PARANOID	7	2
NON-PARANOID	45	34
DEPRESSION		
PSYCHOTIC†	37	25
NEUROTIC	16	10
ANXIETY STATE	9	8
CHARACTER DISORDERS	15	13
OTHERS	16	13
TOTALS	145	105

by symptom

SYMPTOM	NO. IMPROVED
SLEEP DISTURBANCES	36
ANXIETY	30
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AGITATION	8
OTHERS	11
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Clinical Features of Porencephaly

A Review of Thirty-Two Cases

RICHARD W. NAEF, M.D., Philadelphia

Introduction

Although a great deal has been written about porencephaly during the past 100 years, there is much that remains obscure. The clinical recognition of porencephaly is important because it occurs with sufficient frequency to require consideration in the differential diagnosis of focal cerebral lesions. The study of a group of patients is reported in order to clarify some of its clinical features. The patients considered to fulfill the criteria for this study were those with cystic defects of the cerebrum whose lesions were present at, or very shortly after, birth, excluding those with destructive lesions occurring later in life.

Pathology

The term porencephaly has undergone considerable change in its meaning since Heschl [1] first used it in 1859. The lesions included under the loose coverage of porencephaly vary widely. Heschl proposed the term porencephaly to designate specifically the types of circumscribed defects which "have this in common, that in one or several places the cerebral substance is lacking through the entire thickness of the brain and so, if one disregards the purely membranous parts, which fill the defect, there is a canal through the brain which begins on the outer surfaces of the brain and ends in the cerebral ventricles." [31] The interpretation of the term has become broad and ill-defined, including heterogeneous and dissimilar circumscribed defects in the cerebral wall. Various conditions which have erroneously been included among the porencephalies, but must be distinguished from them, are cystic tumors, hemiatrophy of the brain, hydrocephalus, focal cortical atrophy, and cysts of old softening occurring later in life.

Heschl [1] (1859) stated that porencephalic defects are always associated with other anomalies of the cerebrum and are the result of a genuine disease of the brain occurring during its development, and probably not the result of an arrest of development, but he failed to state the cause of the porencephaly. Later Heschl [2] (1868) proposed that porencephaly might be due to a regressive destructive process occasioned by occlusion of cerebral vessels. Since then the theory that most cases of porencephaly appear to result from circulatory disturbances, with subsequent ischemia and necrosis, or from hemorrhage prior to or associated with birth has been widely developed and supported by several clinicopathological studies. Kundrat [3] (1882), after restudying Heschl's works and adding a number of his own cases, concluded that all porencephalies were due to necrotic softening following circulatory disturb-

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From the Department of Neurology, Jefferson Medical College.

ances, leaving the arachnoid roofing and ependymal floor intact, owing to an independent blood supply. He believed that most such defects are congenitally present but may occasionally develop later.

There developed after this the belief that infection was responsible for porencephaly. Strümpell [4] (1884) concluded that some porencephalic defects were due to encephalitis in infancy, and his views were supported by Limbeck [5] (1886). Schultze [6] (1885) was the first to suggest intrauterine infectious encephalitis as a cause. Virchow [7] (1857) had previously shown the existence of fetal encephalitis with secondary changes present at birth. An interesting relationship between infectious and occlusive vascular processes was demonstrated by Globus [8] (1921), who reported the pathological findings in a case of bilateral porencephaly, in which the cystic defects were secondary to meningoencephalitis, resulting in strangulation of pial vessels by pronounced leptomeningeal fibrosis. Inflammatory conditions, such as tuberculosis [9] (Winterode and Lewis, 1923) and syphilis [10] (LeCount and Semarak, 1925), have been related to the development of porencephaly, possibly by vascular embarrassment.

A third concept of the pathogenesis of porencephaly was introduced by Schattenberg [11] in 1889, who stated that some porencephalies are the result of arrest of development. His study was based solely on a study of gross specimens. A year later Sachs and Peterson [12] (1890) argued that porencephaly was a secondary condition and that little was known about the cause. Kahlden [13] (1895) was influential in defending the distinction of "genuine" or developmental porencephalies from embolic, traumatic, or other forms. Messig [14] (1904) disagreed and concluded that all porencephalic defects were the result of destructive lesions. LeCount and Semerak [10] (1925) stated that the cause of cystic developmental defects was a genetic abnormality or injury of the germ plasm, before fertilization. They also believed that cerebral cysts could result from congenital vascular defects. Cohn and Neumann [15] (1946) reported a case of bilateral cerebral cystic defects believed to be due to a primary neuronal dysplastic process, since there were vessels present ostensibly capable of functioning in the defective area of one hemisphere. They believed that if vascular occlusion occurred early enough in the development of the brain, the dependent area could suffer maldevelopment, or even agenesis, and that this type of maldevelopment could not be differentiated from the maldevelopment resulting from defects in the neuronal anlage.

Many investigators, including Holtby [16] (1920), Penfield [17] (1927), Ghizzetti [18] (1931), Patten and Alpers [19] (1933), Patten, Grant, and Yaskin [20] (1937), and Evans and McEachern [21] (1938), have stated that vascular disturbances, such as hemorrhage, embolism, and thrombosis, may lead to porencephaly. The importance of trauma was emphasized by Jaffé [22] (1929), who held trauma during either intrauterine life or at birth to be the commonest cause. He suggested that, in addition to the direct traumatic injury of the brain, circulatory disturbances in the large veins from a damming back of the blood in the sinuses were of great importance in the development of porencephalic defects. Marburg et al.[23,24] (1944 and 1945) demonstrated cases in which impediment of venous drainage resulted in porencephalic defects, especially at birth and during fetal life, producing cysts of softening with scar formation. Other cases of porencephaly due to circulatory disturbances related to intrauterine and birth trauma have been reported in detail by Strom-Olsen [25] (1931), Pendergrass and Perryman [26] (1946), and Christensen and Schondel [27] (1946). Penfield [28] (1936) stated that porencephaly could result from repeated episodes of localized vascular spasm as seen after convulsions and that cysts secondary to thrombosis occur in febrile convulsions and dehydration. Eisenstein and Taylor [29]

(1941) reported a case in which arteriographic studies demonstrated marked obliterative involvement of the vessels in relation to a congenital cerebral cyst, and they offered this as evidence that porencephaly was secondary to vascular maldevelopment or to occlusion related to intrauterine meningoencephalitic changes.

Yakovlev and Wadsworth[30] (1946), in an exhaustive study which included detailed pathological study of their own cases, divided all porencephalies into two major groups based on the manner of their formation, or their "formal origin." These include (1) "encephaloclastic porencephalies," representing circumscribed defects in the cerebral wall which arises as the result of destruction of cerebral tissue, occurring at any time and from whatever cause, such as trauma, circulatory disturbances, or inflammatory or degenerative processes; and (2) "schizencephalies," which represent true clefts formed in the brain as the result of a failure of development of the cerebral mantle and found in zones of cleavage of the primary cerebral fissures. These clefts are true congenital malformations, the result of agenesis or inhibition of the growth and differentiation of the medullary tube.

The pathological changes of porencephaly have been thoroughly described by many authors. These include the studies of Globus,[8] LeCount and Semerak,[10] Cohn and Neumann,[15] Holtby,[16] Jaffé,[22] Marburg,[23,24] Pendergrass and Perryman,[26] Christensen and Schondel,[27] and Yakovlev and Wadsworth.[30] Although the pathological findings vary considerably, the lesions fall into two main groups: those secondary to destructive processes and the developmental malformations. The destructive lesions are defects in the cerebrum resulting from necrotic softening. They show a loss of nerve cells, myelinated fibers, and ependyma, with scar tissue formation consisting of glial proliferation, chiefly fibrous astrocytes. When necrosis occurs during fetal life, the glial response may be slight or absent, and the connective tissue reaction from blood vessels may predominate. The convolutions bordering on the cystic defect are usually atrophic and either partially or completely replaced by sclerosis. The arachnoid and connective tissue from blood vessels usually proliferate to obliterate the original communication of the cyst with the subarachnoid space. Some porencephalies fail to communicate with the ventricle, there being a layer of cerebral substance between the cyst and the ventricle. Cysts of a destructive origin may be bilateral but are usually asymmetrical in position and extent.

The cystic developmental malformations are clefts of varying widths, extending partially or completely through the cerebrum. They are frequently bilateral and symmetrical. Many such defects are associated with hydrocephalus, which may be diffuse or in the form of a local dilatation of the lateral ventricles, with considerable distortion of the existing brain structures. Adjacent to the cystic defect other cerebral structures are incompletely developed. The direct peripheral projections of the missing cerebral structures are incompletely developed or absent in the brain stem and cord. The primary lesion in such instances is dysgenesis of the cerebral mantle, so that both parenchymal and supportive elements are absent in the cyst and incompletely developed in adjacent areas. There is no evidence of glial scar. Microgyria without sclerosis is usually found surrounding the cavities, and abnormal immature cortical architecture of varying degree may occur in other parts of the brain.

Pathological material in this series was available in four cases. All four cysts had their origin either prior to or incidental to birth and were consistent with healed destructive lesions. In three cases the cyst wall and overlying gyri and leptomeninges were removed for study. The specimens included the temporal lobe and angular gyrus in one instance and portions of the parieto-occipital and frontoparietal junction areas in the other two. Each specimen

consisted of an irregular-shaped cyst with a thick, firm wall and a smooth lining continuous with the lateral ventricle. The adjacent gyri were shrunken, distorted, and firm. The overlying pia-arachnoid tissue was thickened and opaque. Microscopically, each wall was composed of dense fibrillary astrocytic tissue, a number of small blood vessels, and varying amounts of collagenous and fibrous connective tissue extending from the vessels. In some areas ependymal cells were seen lining the cyst, and in the adjacent ventricle there was gliotic thickening of the subependymal plate. The cytoarchitecture of the atrophic gyri was distorted, consisting of a few scattered, shrunken, dark or pale neurons, void of Nissl substance, and a diffuse increase in astroglial cells and fibrils. In one lesion there were extracellular granules of hemosiderin. The white matter was atrophic and sclerotic. The overlying pia-arachnoid was thickened by collagenous and fibrous connective tissue with an increased vascularity. Phagocytic cells containing degenerated blood pigments and a moderate perivascular mononuclear-cell response were seen in one specimen. There were fibrous adhesions between the sclerotic cortex and the thickened meninges in all cases. The fourth specimen was biopsy tissue of the meningeal portion of a cyst wall, which revealed only thick fibrous and collagenous connective tissue, with no inflammatory response or other tissue elements.

Definition and Material

The term porencephaly in this study is used for cystic defects in the cerebrum communicating either with the ventricle or with the subarachnoid space or with both, due to a developmental malformation or to a destructive lesion. The 32 cases to be reported have been limited to lesions occurring prior to, during, or shortly after birth. There were 20 male and 12 female patients. For the purpose of this study, "cysts of old softening" resulting from etiological factors occurring later in life, such as trauma, circulatory disturbances, and inflammatory and degenerative processes, have been excluded.

TABLE 1.—*Presumable Occurrence of Lesion Resulting in Porencephaly*

	No.
Prenatal	17 (53%)
Birth injury	7
Postnatal (head trauma)	1
Unknown	7

Among a larger number of patients with porencephaly studied at Jefferson Medical College Hospital during a 14-year period ending with 1956, there were 32 on whom adequate records were available for this study. An effort has been made to evaluate the clinical features of these cases.

Etiology

Some information concerning the etiology can be obtained from the evaluation of possible causal influences occurring during the intrauterine period, birth, and early life. Of the 17 patients in whom the lesion presumably occurred during intrauterine life, there were 3 whose mothers had toxemia of pregnancy and whose deliveries were premature. Premature delivery was the only contributory factor in the histories of two patients. After five days of intermittent labor, one patient was delivered, weighing 4 lb. Another patient, delivered spontaneously at term, was the 18th child of a 43-year-old woman, who had irregular bleeding throughout the pregnancy. There were 10 other patients considered to have congenital lesions, since gestation and birth were normal and no illness occurred prior to the onset of symptoms which could account for the porencephalic lesion.

Birth injury occurred in seven instances. Four of these patients had known injuries; two were members of multiple births and were delivered with difficulty, and one had a focal motor seizure 24 hours after delivery and was unresponsive for four days. One patient with a depressed right occipital skull fracture at one month of age was the only case included in this series with a

known postnatal cause. There were seven patients in whom the occurrence of significant etiological factors was not known. Three of these had normal gestation and delivery, but the early medical histories were not known. The facts concerning the prenatal period and delivery of four patients were unknown.

Symptomatology

Age.—With respect to onset, symptoms ranged from those incidental to birth through those beginning at 44 years of age, indicating a considerable latency in the development of symptoms. In the group of 24 patients whose lesions may be presumed to have been present at birth there were 4 in whom symptoms were present at birth and 11 others in whom they began within the first year. The symptoms of porencephaly in most patients appeared in an additive fashion and progressed in severity. Table 2 indicates the ages, by decades, at which the initial symptoms appeared and at which the symptomatology became complete.

The onset of symptoms was within the first year of life in only 14 patients. The latest onset of initial symptoms occurred at 44 years of age.

The onset of neurological symptoms presumably related to the porencephalic lesion does not correlate coincidentally with the pathogenesis of the lesion. In most instances the symptoms became apparent one or more years after the lesion evidently was in existence.

The diagnosis of porencephaly was established at ages ranging from 6 months to 50 years.

TABLE 2.—*Appearance of Symptoms*

Decade	Onset of Initial Symptoms	Completion of Symptomatology
1st	25 (78%)	24 (75%)
2d	1	2
3d	3	3
4th	1	1
5th	2	2

TABLE 3.—*Age at Time of Diagnosis*

Decade	No. of Patients
1st	7
2d	10
3d	8
4th	4
5th	2
6th	1

It is evident from Table 3 that in the majority (78%) of the patients it was not until adolescence or later that the symptom complex became sufficiently pronounced to force adequate study for establishment of the diagnosis. The diagnosis was established within the first year of life in only two instances.

Latency.—The latency of establishment of the diagnosis after the onset of symptoms extended from 6 months to 44 years.

TABLE 4.—*Latency of Diagnosis After Onset of Symptoms*

Less than 1 yr	3
From 0 to 9 yr	12
From 10 to 19 yr	12
From 20 to 29 yr	7
From 30 to 39 yr	1

These figures would seem to indicate that in the majority of instances (91% with latency over one year) the initial and early subsequently developing symptoms of porencephaly are not sufficiently severe to lead the patients to adequate study of their problem.

Initial Symptoms.—The initial and presenting symptoms to appear during the course of the illness varied considerably, as indicated in Table 5.

TABLE 5.—*Initial Symptoms of Porencephaly*

Symptom		No. of Patients
Spastic weakness		14
Hemiplegia	7	
Hemiparesis	2	
Monoparesis	4	
Quadraplegia	1	
Seizures		13
Focal motor	5	
Generalized	4	
Adversive	2	
Psychomotor	1	
Petit mal	1	
Delayed speech development		3
Homonymous visual defects		2

TABLE 6.—*Subsequent Symptoms of Porencephaly*

	Instances	No. of Patients
Seizures		24
Generalized	8	
Focal motor	9	
Focal motor and sensory	3	
Focal sensory	1	
Psychomotor	3	
Petit mal	2	
Adversive	2	
Visual perceptive	2	
Spastic weakness		10
Hemiparesis	9	
Monoplegia	2	
Delayed unilateral extremity growth		10
Atrophy of fully developed limbs		1
Mental retardation		9
Delayed speech development		4
Unilateral sensory loss		2
Organic mental syndrome		2
Headaches, independent of seizures		2
Amblyopia		1
Diminished visual acuity		1
Unilateral squint		1

Of these initial symptoms, weakness was the commonest (44%), with seizures occurring only slightly less commonly (41%). The initial symptom could be considered as indicative of a localized cerebral lesion in 22 patients (67%).

Subsequent Symptoms.—Subsequent symptoms, or those developing at a variable period after the initial symptom, occurred in 28 patients (88%) and were multiple in all but 4 of these. Table 6 indicates the type and frequency of the subsequently developing symptoms.

The majority of these symptoms found in 24 patients (75%) may be interpreted as indicative of a focal brain lesion. Considering both the initial and the subsequent symptoms, they were indicative of a focal cerebral lesion in 29 patients (92%).

Course of Symptoms.—The symptoms of porencephaly varied greatly in their duration, severity, and course among this group of patients. No attempt has been made to indicate the duration or severity of the individual symptoms. The symptoms varied in duration from a few weeks to many years. The appearance of symptoms was in an accumulative fashion in 29 patients, leaving only 3 in whom all symptoms developed simultaneously. Table 7 indicates the number of individual symptoms and the period of latency following the onset of the initial symptom of each patient. Symptoms were accumulative in 29 patients, and

TABLE 7.—*Latency of Appearance of Subsequent Symptoms*

Period of Latency	No. of Symptoms
Within 1 yr.	7
Within first 10 yr.	31
Within second 10 yr.	20
After 20 yr.	2

the latency of their appearance ranged from 1 month to 29 years.

The course of each symptom is important to the natural history of this disease and in most instances could be evaluated in terms of whether it was progressive, regressive, recurrent, or static. Seizures were the commonest symptom, since they occurred in 46 instances as various types in a total of 30 patients. The course of the seizure history of the 30 patients and the individual seizure types are outlined in Table 8.

Spastic weakness, present in 23 patients as the second commonest symptom, was progressive in 8 patients and static after appearance in 15 patients. Hemiplegia was static in seven instances. Hemiparesis was progressive in six instances and static in six. Monoparesis was progressive in two patients and static in one. Quadraplegia was static in one patient.

Considering all symptoms exclusive of seizures and spastic weakness, there were 33 which could be considered static throughout their course and 8 which were progressive. Table 9 indicates the symptoms and their course.

In reviewing the course of each patient's symptomatology, it becomes evident that the clinical course of the symptoms was progressive in severity in 26 patients (81%) and static in only 6 patients. It will be

TABLE 8.—*Course of Seizures*

	Progressive	Regressive	Static
Patients' history of seizures	24	1	5
Total incidence of seizures	35	3	8
Focal motor	11	1	3
Focal motor and sensory	3	0	0
Focal sensory	1	0	0
Generalized	8	1	5
Psychomotor	4	0	0
Adversive	4	0	0
Petit mal	2	1	0
Visual perceptive	2	0	0

TABLE 9.—*Course of Symptoms*

	Progressive	Static
Delayed speech development and defective speech	0	5
Delayed speech development with no subsequent defect	6	3
Mental retardation	1	10
Organic mental syndrome	2	0
Delayed unilateral growth of limbs	0	9
Wasting of arm in adult life	1	0
Amblyopia	0	1
Diminished acuity and squint	0	2
Homonymous visual defect	2	0
Diminished unilateral sensation	0	3
Headaches, independent of seizures	2	0

recalled that the symptoms appeared in an accumulative manner in 29 patients (91%).

It is interesting to note the nature of the symptoms which precipitated hospitalization, leading to the pertinent investigation resulting in the establishment of the diagnosis. In 27 patients (84%) the chief complaint was of seizures, which were recent in onset in 4 and progressive or uncontrolled on medication in the other 23 patients. One patient each presented with the chief complaints of unilateral weakness, delayed unilateral limb growth, homonymous visual field defect, and mental deterioration.

Signs

The signs present on admission during which the diagnosis of porencephaly was established lend themselves to some interesting correlations. Twenty-nine patients (91%) had signs indicative of focal unilateral cerebral lesions. Spastic weakness with hyperactive reflex changes was found most commonly, existing unilaterally in 23 patients (72%) and bilaterally in 2. Delayed unilateral limb growth was found in 14 patients, in each case existing with weakness of the involved limbs. Atrophy of a fully developed arm was found in one patient. Unilateral sensory disturbance consistent with a parietal lobe lesion was evident in 11 patients, occurring in each instance in limbs which were also found to be weak. Homonymous visual field defects were demonstrated in seven patients and existed as a transient postictal finding in one patient who had visual perceptive seizures.

Various other findings were indicative of either diffuse nonspecific encephalopathy or lesions of the eyes or their musculature. Aphasia was not evident, but one patient had dysarthria and three revealed severe developmental speech defects. Mental retardation was evident in 19 patients. One patient manifested a moderately advanced organic mental syndrome. Amblyopia was present in an infant who had a quadriplegia. A unilateral visual acuity defect of 20/200 in one patient was associated with a laterally deviated concomitant strabismus. Another patient had vision of 5/200 in each eye and an alternating strabismus. A right external rectus paresis was present in one instance. The neurological examination was considered to be normal in one patient who complained of a 12-year history of generalized convulsions, beginning at 22 years of age.

Laboratory Studies.—Serological tests for syphilis were negative in 29 patients. They were not done in two, and the test was positive in one man who had no clinical evidence of syphilis. The cerebrospinal fluid was studied in all but one patient and was normal in regard to pressure, cell count, and complement fixation in all instances. One patient had a spinal fluid protein of 51 mg.% and a colloidal gold reaction of 4432220000; the serological tests for syphilis were nonreactive, and there was no clinical evidence of syphilis. The spinal fluid proteins were 68 and 124 mg.% in the only instances in which the protein was elevated.

Visual field studies revealed four instances of left and three of right homonymous hemianopsia. The visual fields were full in the patient who manifested a homonymous visual defect during a short postictal period.

The skull roentgenograms of 24 patients (75%) were interpreted as normal. The location of bony abnormalities seen in eight studies corresponded with the porencephalic lesion as later demonstrated. Rarefaction or thinning of the parietal bone of one side was seen extending over an area of several

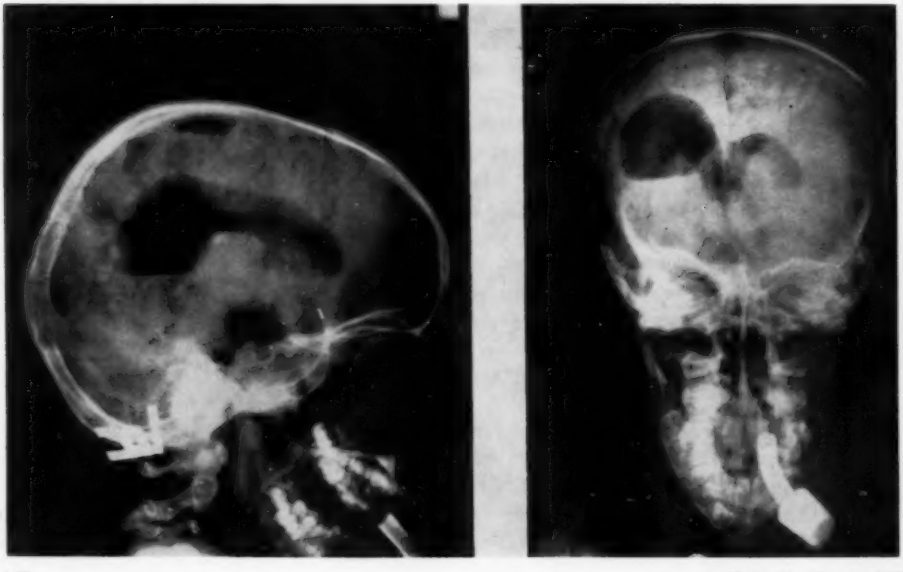
centimeters' diameter in six instances (Fig. 4). One patient who had such thinning also had elevation of the petrous pyramid on the same side, and another had an asymmetrical skull with enlargement of the same side of the calvaria. One skull was asymmetrical with underdevelopment of the significant side. In one patient there was a large plaque of calcification in the parietal area, thought to be in the subdural space overlying the cyst (Fig. 6).

Electroencephalography was performed on 26 patients and was normal in 4 instances. Of the 22 abnormal electroencephalograms, there were 4 with generalized paroxysmal cerebral dysrhythmia, 1 with poorly developed rhythm and low voltage generally, and 1 with generalized large slow waves, leaving 16 records indicative of focal activity. Two of the foci proved to be located over the hemisphere opposite the porencephalic lesion. Fourteen of the EEG studies disclosed foci corresponding closely to the location of the cyst. There were no predominant characteristics of the focal activity, since there were two multiple-spike foci, three foci of depressed activity, three slow-wave foci, one focus of high-voltage slow waves, one of high-voltage sharp waves, one of slow-and-fast waves, and three of unspecified types.

Arteriography was performed on four patients. One carotid arteriogram done on the same side as a large frontal lobe cyst revealed pronounced attenuation of the caliber of the middle cerebral artery with incomplete filling of its branches (Fig. 8). Another carotid arteriogram was normal on the side corresponding to a large parietooccipital cyst. A vertebral arteriogram done on a man with a frontoparietal cyst was normal. Another vertebral arteriogram done on a patient with a unilateral occipital lobe cyst failed to reveal either posterior cerebral artery.

Each of the 32 patients underwent pneumoencephalography, which revealed the porencephalic defect in all but one instance. In this case a large frontoparietal cyst was disclosed by exploration of the hemisphere, in which there was no ventricular air filling (representative studies, Figs. 1 through 8).

Fig. 1.—A left parietal porencephalic cyst in a boy with right-sided motor seizures and bilaterally present Babinski sign, ankle clonus, and hyperactive deep tendon reflexes of the legs.



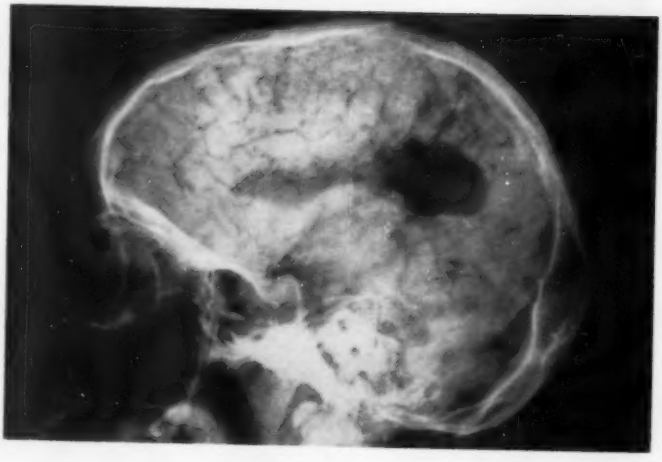
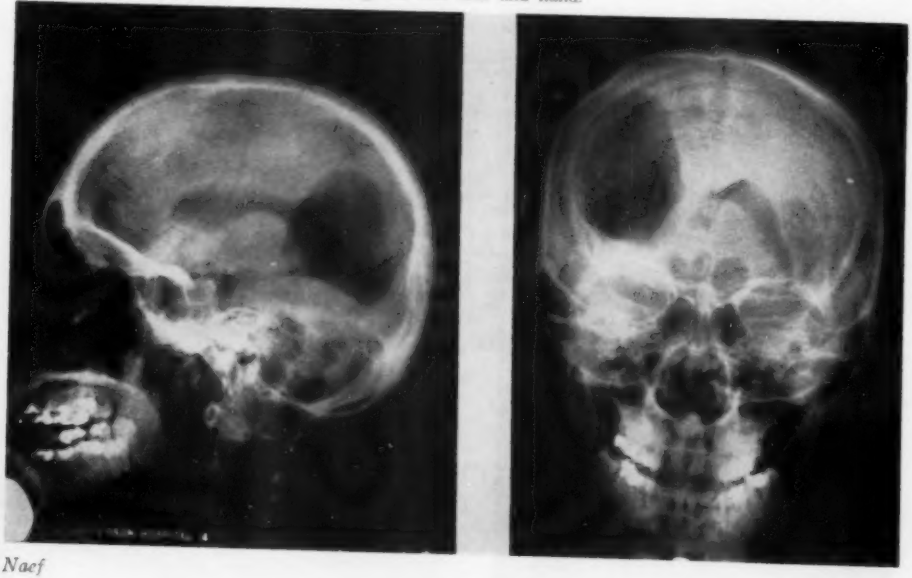


Fig. 2.—Dilatation of the left lateral ventricle and porencephaly in the parieto-occipital area found in a young man with right hemiparesis, right-sided focal motor, psychomotor and generalized seizures, and mental retardation.

Table 10 indicates the anatomical features as disclosed by pneumoencephalography and surgical exploration. It could not always be decided whether the cysts that communicated with the lateral ventricles also communicated with the subarachnoid space, but in three pneumoencephalograms the air in the cysts appeared to be continuous with air in the enlarged subarachnoid spaces overlying atrophic gyri adjacent to the outer extent of the cysts. The one cyst disclosed by exploration but not seen in a pneumoencephalogram did not communicate with either the ventricle or the subarachnoid space, since it was covered by thickened meninges that were adherent to the adjacent cortex.

Clinical Correlation with Location of Porencephaly.—The location of the cyst corresponded laterally to the hemisphere in-

Fig. 3.—Right parieto-occipital porencephaly in a young woman with weakness, hypoplasia, and cortical sensory deficit involving the left arm and hand.



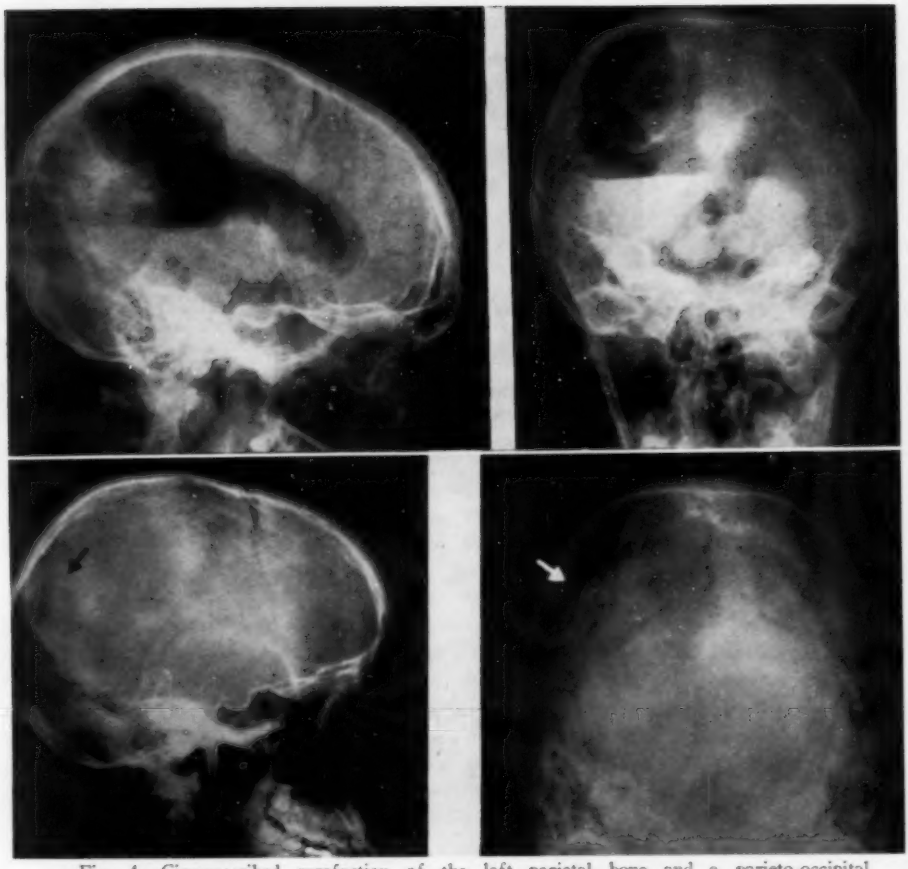
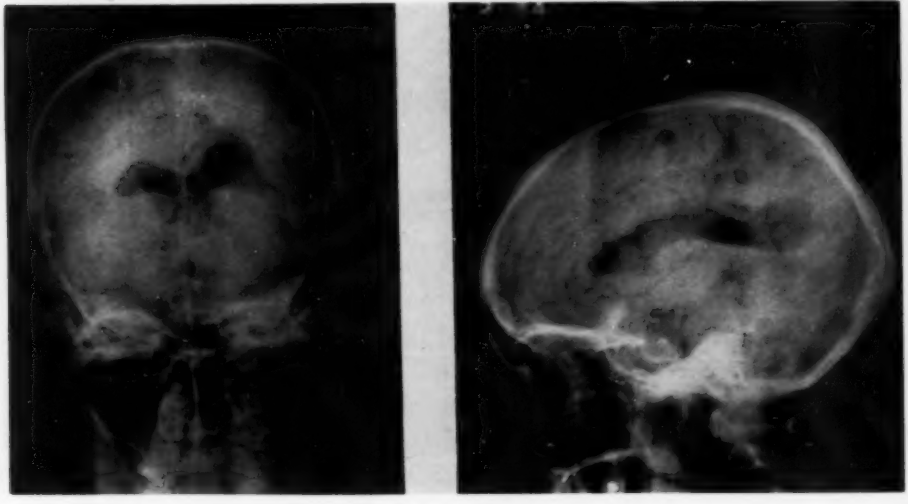


Fig. 4.—Circumscribed rarefaction of the left parietal bone and a parieto-occipital porencephalic cyst in a young man with visual perceptive seizures in the form of flashing white lights in the right hemianopic fields, occurring both independently of and preceding adversive and right-sided focal motor seizures.

Fig. 5.—A left occipital lobe porencephalic cyst in a woman with a right homonymous hemianopsia.



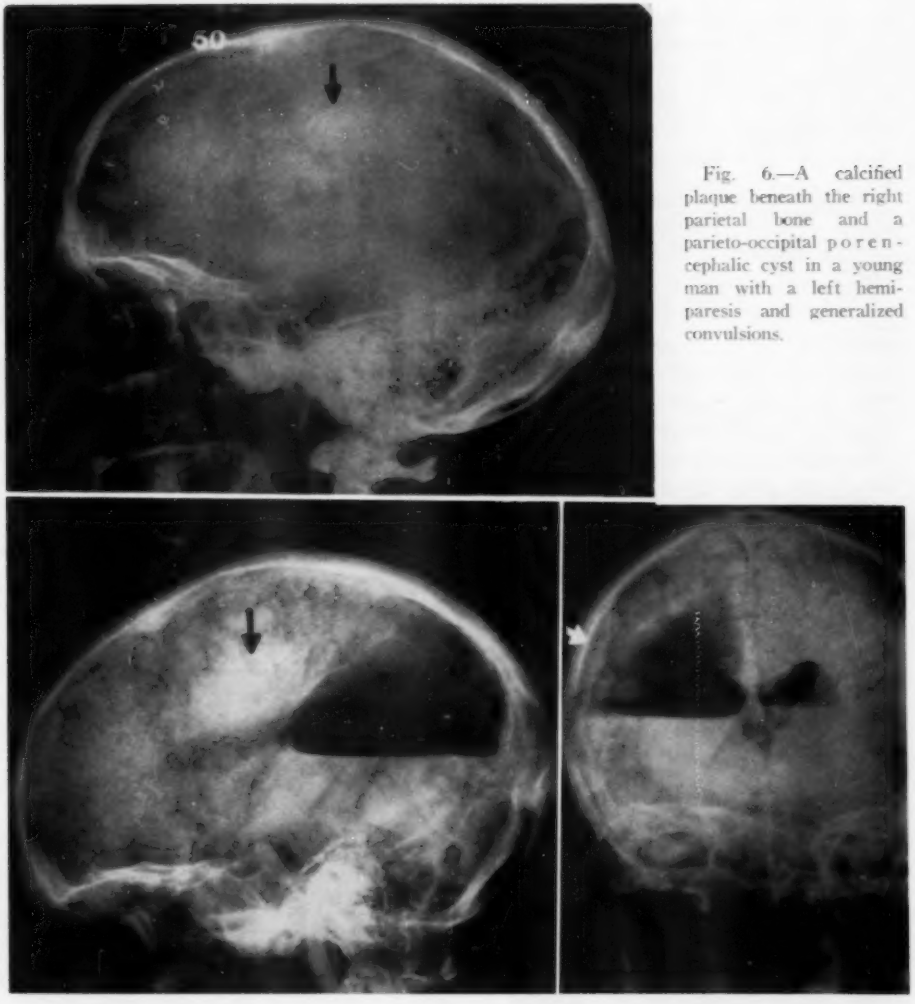


Fig. 6.—A calcified plaque beneath the right parietal bone and a parieto-occipital porencephalic cyst in a young man with a left hemiparesis and generalized convulsions.

TABLE 10.—*Pneumoencephalographic Features*

Anatomical Feature	No. of Patients
A. Location in regard to subarachnoid and ventricular spaces	
1. Cyst communicated with ventricle	31
2. Cyst did not communicate (found by surgery)	1
B. Appearance of lateral ventricles	
1. Dilatation of both lateral ventricles	6
2. Dilatation of lateral ventricle adjacent to cyst	11
3. No ventricular dilatation	15
C. Location of cyst in hemisphere	
1. Bilateral, frontal	1
2. Bilateral, frontal and occipital	1
3. Frontal	6
4. Parietal	3
5. Frontoparietal	6
6. Temporoparietal	1
7. Temporal	3
8. Occipital	3
9. Parieto-occipital	8

dicated by the symptoms and signs in 29 patients (91%). The cyst involved the actual lobe indicated clinically in 22 instances (69%), and it was found to involve an area of the hemisphere other than that clinically indicated in 7 cases. The cyst was located in the hemisphere opposite that clinically indicated in one patient, but there was generalized dilatation of the lateral ventricle on the clinically significant side. There were single porencephalic lesions found in

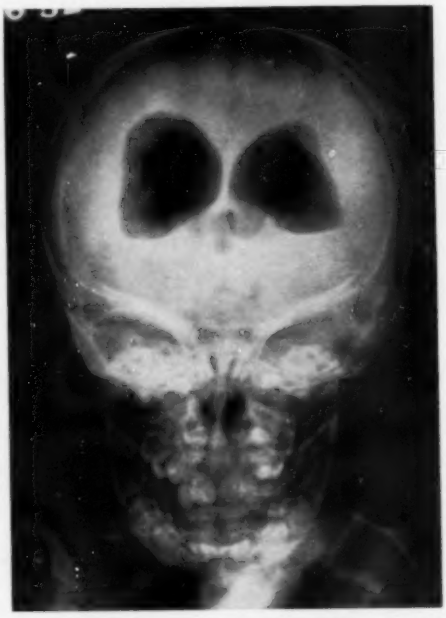
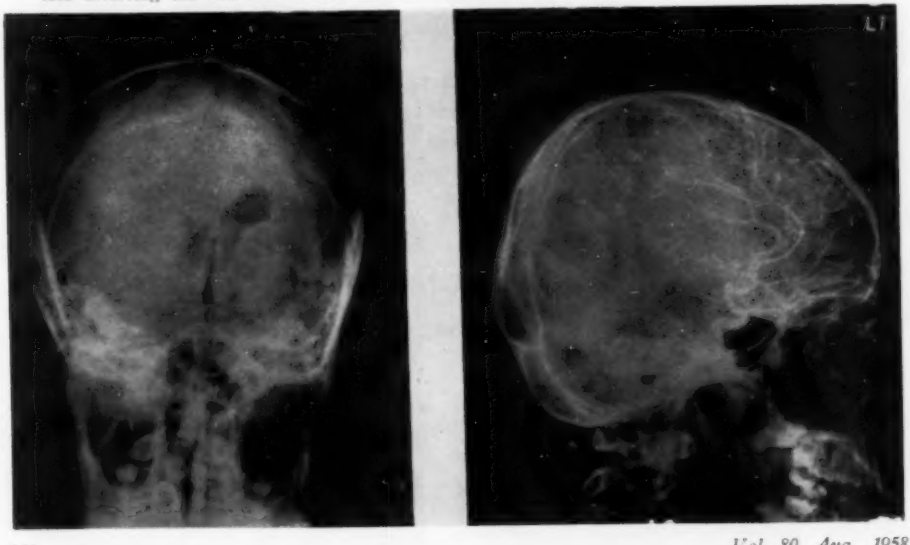


Fig. 7.—Dilatation of the lateral and third ventricles and bilateral frontal lobe porencephaly in a boy 7 months of age with congenital quadraplegia.

Fig. 8.—Left frontal porencephalic cyst and attenuation of the left middle cerebral artery in a boy with sensory and motor seizures, spastic weakness, hypoplasia, and cortical sensory loss involving the left extremities.



two patients whose symptoms and signs were not indicative of focal lesions. It becomes evident from comparison of the location of the cyst to the clinical picture that the cystic lesion itself does not account for the symptoms and signs in almost one-third of the patients in this series. The assumption seems inevitable that there must be considerable brain damage other than, and in addition to, the porencephaly itself.

Diagnosis

The question arises as to what collection of data is sufficient to make a presumptive diagnosis of porencephaly. It is evident from analysis of these 32 cases that the factors of diagnostic importance are symptoms and signs indicative of a focal cerebral lesion. Skull roentgenographic findings and EEG changes indicative of a focal lesion may be of some help. Normal skull roentgenographic studies and normal or generally abnormal EEG patterns have no significance and do not tend to rule out the existence of a porencephalic lesion. The cerebrospinal fluid study offers no help in making the diagnosis, since it is usually normal in all respects. Abnormal cerebrospinal fluid findings would be suggestive of a lesion other than porencephaly. No significant information concerning the appearance of arteriograms in this disease is available from this study, since only two were performed outlining the vessels overlying the lesion and one of these was normal in appearance. Although the diagnosis may be suspected on the basis of clinical information and the above-mentioned studies, it remains for the lesion to be actually demonstrated by pneumonencephalography.

In retrospect, the data which would lead to the presumptive diagnosis of porencephaly on the basis of clinical observation alone can be outlined from this series. The occurrence of the lesion resulting in porencephaly may be presumed to have been prior to or incidental to birth in all but one patient, in whom the lesion occurred at one month of age. Cystic or atrophic focal lesions that can be attributed to known etiological factors occurring later in life have been excluded from our concept of this disease, and the diagnosis in these cases would be that of the primary disease, not porencephaly. The onset of symptoms was within the first year of life in less than half of these patients; hence the absence of an early onset would not tend to rule out the diagnosis of porencephaly. The severity of the initial symptoms is not a reliable index, since it varies greatly and is usually of a degree that does not force adequate study and diagnosis early in the course of illness. The lack of serious or severe symptoms early in the course is indicated by the fact that there was a latency of diagnosis after the onset of symptoms of over one year in 91% of these patients and a latency of over 10 years in 63%. The symptomatology is consistent with a focal cerebral lesion in the large majority (92%) of proved cases of porencephaly, the commonest symptoms being spastic weakness, focal seizures, delayed unilateral body growth, unilateral sensory loss, and homonymous visual field defects.

The characteristic course of the symptoms of porencephaly is both accumulative (91%) as to the number of symptoms of each patient and progressive (81%) in severity. The signs upon neurological examination are indicative of focal unilateral cerebral lesions in most instances (91%). The localizing signs correspond closely with the symptoms and consist most commonly of spastic weakness, delayed unilateral body growth, cortical sensory disturbances, and homonymous hemianopsia. The age when the patient appears for study is of little importance diagnostically, since it varies widely, ranging from 6 months to 50 years in this group of patients; however, the majority are young adults (12 between 20 and 39 years of age) or adolescents (10 between 10 and 19 years). Given a patient whose clinical picture corresponds to these characteristics, a presumptive diagnosis of porencephaly may be made. Focally abnor-

mal EEG studies are found in about one-half of the cases, but the absence of focal discharge has no significance. Roentgenographic skull changes, such as erosion of the inner table of the calvaria, are not common but when present are strongly suggestive of porencephaly, although not pathognomonic. Pneumoencephalography remains then as the only procedure which will confirm the diagnosis short of surgical exploration.

Treatment and Outcome

Twenty-five patients treated with anticonvulsive drugs experienced improvement in the frequency or severity of seizures during the period of follow-up, which ranged from a few days to two years. There were four patients treated with anticonvulsive drugs and one who remained untreated who did not improve while under observation. There is no evidence that there has been any improvement of strength, sensation, maturation of limbs, or vision in patients with such symptoms. Surgical procedures consisted of simple exploration by trephination and biopsy of thickened meninges overlying the cyst in one patient and exploratory craniotomy in another instance without opening the cyst wall. Incision and drainage of the cyst was performed in two instances. Excision of the cyst wall was performed on two patients, and one underwent removal of a cystic temporal lobe. Five of these patients were treated with anticonvulsive drugs following surgery, with improvement of their seizure state. The patient who underwent temporal lobectomy has been free of psychomotor seizures without drug therapy for two years.

Summary

A series of 32 cases in which the diagnosis of porencephaly has been established is presented in order to indicate the clinical features of the disease. The term porencephaly is used to indicate nontumorous cystic lesions of the brain communicating with the ventricles and/or the subarachnoid space, resulting from either developmental or destructive lesions. It is not possible to assign each case to one or the other pathogenic group on a clinical basis. The large majority of the cases presented belong to the group of destructive lesions, or "encephaloclastic porencephalies" of Yakovlev and Wadsworth. The case in which symmetrical bilateral frontal cysts were demonstrated is the only one which can reasonably be considered as belonging to the developmental, or "schizencephalic," group. We have limited the use of the term porencephaly to those cases in which the etiological lesion occurred prior to, incidental to, or shortly after birth. The clinical features of porencephaly as a disease consist, in a majority of instances, of symptoms referable to a focal cerebral hemispheric lesion, with the clinical onset at a variable time after occurrence of the underlying process, and developing with an accumulative and progressively severe course. In most cases of porencephaly the signs are indicative of focal cerebral lesions which correlate well with the symptoms. The clinical picture, in the majority of patients, early in its course, is mild to moderate in degree, so that it does not precipitate adequate study until adolescence or early adulthood. The only symptoms that apparently improve were seizures of various types, which did so after excision of the cysts or upon adequate anticonvulsive therapy. The pathogenic changes which account for the clinically progressive characteristics of this disease remain to be disclosed and explained.

Department of Neurology, Jefferson Medical College.

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Cerebrospinal Fluid Transaminase and Lactic Dehydrogenase Activities in Neurologic Disease

JOSEPH B. GREEN, M.D.; HENRY A. OLDEWURTEL; DESMOND S. O'DOHERTY, M.D., and FRANCIS M. FORSTER, M.D., Washington, D. C.

Clinical and experimental studies have shown that destruction of central nervous system parenchyma is associated with increased activity of the enzyme glutamic-oxalacetic transaminase * in the cerebrospinal fluid.[1,2] In a recent survey of cerebrospinal fluid transaminase in neurologic diseases, we reported this activity to be elevated in the majority of cases of cerebral infarction studied.[3] High levels were usually reached by the third day of the disease; a pattern of gradually increasing activity was present in several patients subjected to repeated lumbar punctures over a 30-day period. No changes in serum levels were observed. Conversely, several patients without neurologic symptoms or signs, but with hepatic or muscle necrosis, had extremely high serum activities and normal cerebrospinal fluid levels.

The cerebrospinal fluid transaminase activity was not significantly increased in 14 cases of primary brain tumor.[3] Because of this difference in enzyme findings between cerebrovascular disease and primary brain tumor, the determination of transaminase activity in the cerebrospinal fluid was thought to be potentially valuable in diagnosis, and the study was expanded to include more cases. In addition, the lactic dehydrogenase activity of each spinal fluid was determined. It has been reported that the activity of this enzyme is increased in the sera of patients with certain neoplastic diseases,[4] as well as in cases of myocardial and hepatic necrosis.[5]

A few patients with acute forms of multiple sclerosis were found to have moderate elevations of spinal fluid transaminase activity. This series was also extended to evaluate the relation, if any, that was present between this abnormality and the activity of the demyelination.

Finally, we have attempted to characterize further changes in cerebrospinal fluid transaminase observed during pneumonencephalography.

Materials and Methods

Cerebrospinal fluid transaminase activity was determined spectrophotometrically at 37 C. A. Beckman Model DU spectrophotometer with thermospacer accessory was used. The changes in optical density were followed at appropriate intervals so that assurance could be had that each reaction was of zero order. The exact methodology is reported in detail elsewhere.[3] In accordance with the conviction that enzymatic activity should be expressed in basic units equating different methods, results were expressed in terms of micromoles of product (oxalacetate) formed per hour per quantity of cerebrospinal fluid. The quantity selected was 100 ml. for ease of reporting and interpretation. The transaminase activity and standard deviation of the spinal fluids of 60 subjects free from neurologic illness averaged $43 \pm 12 \mu M$ of oxalacetate formed per

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From the Department of Neurology and the Clinical Chemistry Laboratory, Georgetown University Medical Center, Washington, D. C.

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* For brevity, glutamic oxalacetic transaminase will be referred to as "transaminase."

hour per 100 ml. at 37 C, with a range of 25μM to 62μM.

Recently, a survey of lactic dehydrogenase (and transaminase) activity in spinal fluid has been published by other authors, who presented results many of which contradicted the data to be found in this communication.[6] Disagreement extended to control spinal fluid values.

Therefore it was felt necessary to review in some detail the methodology used in determining lactic dehydrogenase activity. Bruns and associates[7] were apparently the first to measure lactic dehydrogenase in the spinal fluid. The assay procedure they used was essentially that introduced by Kubowitz and Ott, in which the catalytic reduction of pyruvate to lactate was followed by measuring the concomitant oxidation of reduced diphosphopyridine nucleotide (DPNH).[8] This oxidation was determined spectophotometrically by recording a decrease in optical density at a wave length of 340 mμ.[9] Fleisher et al. also cite this methodology in their recent report on lactic dehydrogenase in spinal fluid.[6]

When the recommended concentration of pyruvate and DPNH was used and the reaction started with spinal fluid, as described, the data obtained in this laboratory were thought unsatisfactory, because the enzyme kinetics failed to obey a constant order of activity, and also because of the presence of certain interfering reactions. On the premise that zero-order activity is the most desirable and most reproducible activity for a comparative study, an investigation was conducted to determine the conditions necessary for optimum kinetics of lactic dehydrogenase. It is sufficient to indicate here that the concentration of reduced diphosphopyridine nucleotide (DPNH) was the principal limiting factor in the methods used by the authors cited above.

It is probable that the mechanism of lactic dehydrogenase activity requires the formation of a lactic dehydrogenase-coenzyme compound, which subsequently combines with the substrate to continue enzymatic activity. Chance and Neilands have demonstrated the existence of such a compound and have shown that it is highly dissociated.[10] The unfavorable equilibrium in the apoenzyme-coenzyme reaction may explain the lack of zero-order activity found in lactic dehydrogenase reactions using moderate to low concentrations of the coenzyme (DPNH), especially when the enzyme concentration is increased. It was found that by increasing the concentration of DPNH more favorable kinetics were obtained, probably because of an increase in the amount of apoenzyme-coenzyme complex, in accordance with the mass law.

In all spinal fluids so far tested, there was found an endogenous DPNH-oxidizing capacity. This activity may surpass that obtained after the addition of pyruvate. In the majority of instances it did not follow linear kinetics, and in a large number of fluids it was followed until exhausted. It required a minimum of 30 minutes to disappear, as previously reported.[8] In practice, the reaction mixture was permitted to stand 40 to 45 minutes before starting the reaction by adding pyruvate; as a further precaution, it was determined that this activity had ceased prior to continuing the test.

It is evident that when the reaction catalyzed by lactic dehydrogenase is started by the addition of spinal fluid, as in the procedures used by other investigators, a combination of endogenous and lactic dehydrogenase activity is measured. Since the endogenous activities of spinal fluids are different and follow unpredictable kinetics, the results of such methodology will be equally variable and nonspecific.

Owing to the logarithmic limitations of the scale on the Beckman DU spectrophotometer, a high concentration of DPNH is difficult to read. Therefore an artificially high blank has been adopted which in effect will subtract a portion of the density of the unknown reaction mixture. A solution of K_2CrO_4 in dilute alkali, proposed as a stable solution for density calibration by the Na-

tional Bureau of Standards, was used as the blank.[11] Since it has been found unnecessary to provide a spinal fluid or reagent blank in this assay, the above device was considered valid.

The instrument used for all lactic dehydrogenase determinations was a Beckman Model DU spectrophotometer equipped with thermospacers regulating the cell compartment at 37 C. A tungsten lamp was used as a light source.

Reagents

M/10 K_2HPO_4—potassium phosphate buffer, pH 7.4

M/100 sodium pyruvate, dissolved in above buffer

Reduced diphosphopyridine nucleotide, 1 mg/ml., dissolved in above buffer

0.40 gm. K_2CrO_4 per liter of 0.05 N KOH standard blank solution

Procedure

To 1.00 cm. Corex cuvettes were added 2.3 ml. of buffer, 0.4 ml. of DPNH, and 0.3 ml. of cerebrospinal fluid. This mixture stood for 40 to 45 minutes. When endogenous activity had ceased, the lactic dehydrogenase reaction was started with 0.2 ml. of sodium pyruvate. With the spectrophotometer set at zero density with reference to the chromate solution, density readings were recorded at selected time intervals. Good precision was obtained when differences in optical density were 0.02 or more. Equal decrements in optical density indicated that the activity was of zero order.

Spinal fluid was obtained from 10 subjects prior to the administration of spinal anesthesia. These patients were free of systemic or neurologic illness and were undergoing minor surgical procedures. Twenty more patients, later found to have "functional" or "neurotic" ailments, were also studied by lumbar puncture. The average normal lactic dehydrogenase activity and standard deviation for these 30 persons was $68 \pm 15 \mu M$ of lactate formed per hour per 100 ml. of cerebrospinal fluid at 37 C, with a range of $31 \mu M$ to $87 \mu M$.

All spinal fluid specimens analyzed in the series to be reported were collected by lumbar puncture, performed in the usual manner. Red or white blood cells, when present in excess, were found to contribute significant amounts of both transaminase and lactic dehydrogenase to the cerebrospinal fluid "pools" of these enzymes. Cell counts, therefore, were necessary in all cases to ensure that activity measured was of parenchymal origin. Fluids containing over 400 red blood cells or 50 white blood cells per cubic millimeter were centrifuged immediately and decanted. If enzymatic analysis was delayed, spinal fluid was promptly refrigerated, for a loss of activity occurred after four to six hours at room temperature. Both transaminase and lactic dehydrogenase activities were preserved for two weeks if the fluid was refrigerated at 4 C.

Results

Cerebral Infarction.—The criteria for this diagnosis have been summarized previously.[3] They may be restated as (*a*) sudden onset of focal neurologic deficit in an arteriosclerotic patient, (*b*) absence of gross blood or an increased number of white cells in the cerebrospinal fluid, and (*c*) absence of signs and symptoms of increased intracranial pressure. All patients received complete physical and laboratory examinations and were followed by a competent neurologist until death or discharge. Lumbar puncture was performed more than once in at least 25% of the cases.

Table 1 classifies 37 cases of cerebral infarction according to the artery occluded. The cerebrospinal fluid transaminase was elevated in 26, or 70%; the lactic dehydrogenase, in 27, or 73%. The average transaminase value for all cases represented a 216% increase over mean normal activity. The average lactic dehydrogenase activity of the group was 222% above the mean normal cerebrospinal fluid activity of this enzyme. The standard deviation for lactic dehydrogenase was over twice that for

TABLE 1.—*Composite of Cerebral Infarctions According to Artery Occluded*

Artery Occluded	No. of Cases	Transaminase, μM			Lactic Dehydrogenase, μM		
		Mean	S. D.	Range	Mean	S. D.	Range
Internal carotid	4	71	±23	43–105	125	±20	62–217
Middle cerebral	25	94	±35	46–117	147	±83	50–363
Basilar	7	101	±36	49–155	176	±100	71–396
All cases	37	93	±37	43–177	151	±86	50–396
Normals		43	±12	25–62	68	±15	31–87

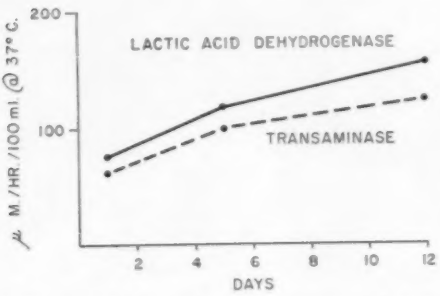

Fig. 1.—Changes in enzyme activity of CSF in case of thrombosis of left middle cerebral artery.

transaminase, reflecting very great activities of the dehydrogenase occasionally encountered (for example, 363μM and 396μM).

Basilar thrombosis yielded the highest levels of both enzymes in this series. The four cases of internal carotid thrombosis had mild symptoms and signs and had averaged three separate attacks each before admission and diagnostic arteriography. The middle cerebral artery occlusions included a wide range of enzyme activities.

In the total number of 37 cases, there were 8 deaths (4 with autopsy) which were attributed to the central nervous system lesion. The mean transaminase and lactic dehydrogenase values for these fatalities were 102μM and 162μM, respectively.

Figure 1 charts the rate of increase of both enzyme activities in the spinal fluid of a man suffering an infarction in the left middle cerebral artery distribution. During this period there was a definite worsening of his clinical signs.

One 63-year-old woman, in whom an internal carotid occlusion was suspected, improved markedly over a two-week period. The initial transaminase, of 78μM, and lactic dehydrogenase, of 155μM, fell to 59μM and 96μM, respectively.

In Table 2 are included all cases of cerebral infarction in which the cerebrospinal fluid transaminase activities were determined, including the 53 cases previously reported. The transaminase activity was increased in 66% of the 90 cases. The average activity of the entire series was

TABLE 2.—*Composite of Cerebral Infarctions According to Artery Occluded*

Artery Occluded	No. of Cases	Transaminase, μM		
		Mean	S. D.	Range
Internal carotid	15	144	±89	43–470
Middle cerebral	61	88	±41	35–260
Basilar	13	116	±46	49–210
Posterior cerebral	1	62		
All cases	90	101	±61	35–470
Normals	50	43	±12	25–62

approximately 235% above the mean normal of 43μM. Inspection of the diagnostic groupings (Table 2) reveals both a high average value and a large standard deviation for the 15 cases of internal carotid occlusion. The transaminase levels ranged widely, correlating well with differences in severity noted in these cases.

In 18 of the 90 cases; the infarctions resulted in death (13 with autopsy). These fatalities had a mean cerebrospinal fluid transaminase of 148μM (range, 49μM to 470μM); two cases had normal levels. Fifteen patients made complete or near-complete recoveries. The average activity in this group was 66μM (range, 45μM to 124μM).

TABLE 3.—*Central Nervous System Neoplasms*

Tumor	Transaminase, μM	Lactic Dehydrogenase, μM
Glioblastoma		
Hemispheric, cerebral	53	124
Hemispheric, cerebral	62	
Hemispheric, cerebral	56	
Hemispheric, cerebral	55	
Astrocytoma		
Hemispheric, cerebral (spinal fluid)	80	155
Hemispheric, cerebral (cyst fluid)	713	16,306
Hemispheric, cerebral	50	
Hemispheric, cerebral	50	
Cord, cervical (infiltrating)	37	127
Medulloblastoma	43	
Meningioma		
Convexity	62	164
Convexity	90	115
Convexity	87	112
Convexity	62	
Sphenoid ridge	68	
Cord, thoracic	71	102
Pituitary adenoma		
Chromophobe	62	102
Chromophobe	68	
Chromophobe	62	
Acoustic neuroma	56	
Carcinoma, sphenoid sinus	68	
Metastatic carcinoma		
Lung to brain (cerebrum)	71	428
Lung to brain (cerebrum)	124	360
Breast to spine (dura)	84	115
Melanoma		
Skin to cerebellum	24	
	Mean S. D.	Range
Transaminase—24 cases	64±19	24–124
Lactic dehydrogenase—11 cases	173±107	102–428

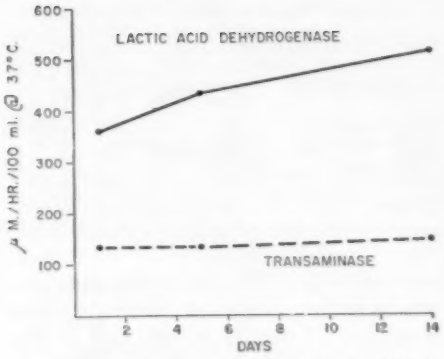

Fig. 2.—Changes in enzyme activity of CSF in case of carcinoma metastatic from lung to brain (autopsy).

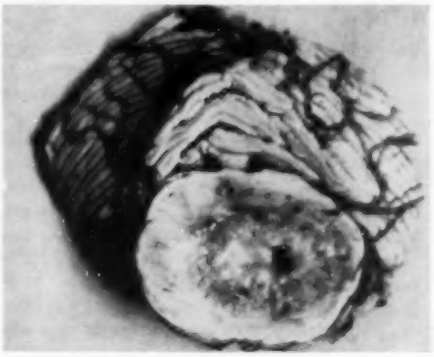

Fig. 3.—Pons in case shown in Figure 2, showing necrosis surrounded by tumor (dark area).

In 39 cases of infarction in the internal carotid or middle cerebral artery distribution manifesting aphasia or parietal lobe signs the average activity was 124μM (range, 46μM to 470μM).

Tumors of the Central Nervous System.—Table 3 lists 24 histologically proved tumors, from 1 of which (astrocytoma) cyst fluid was obtained. Transaminase activity was elevated in 10 cases but was appreciably increased in 3—2 cases of meningioma and 1 of carcinoma metastatic from lung to brain. The average elevation produced by these 10 tumors was 88% above mean normal activity, and the levels ranged from 58% to 180%.

Lactic dehydrogenase activity was determined in 11 cases of brain tumor and was elevated in all cases. The average elevation over the mean normal was 154%; the increase ranged from 50% to 530%.

Figure 2 depicts the activity of both enzymes in a patient with multiple cerebral and brain-stem metastases from a bronchogenic carcinoma (proved at autopsy). The lactic dehydrogenase gradually increased until death, whereas the transaminase activity remained close to the initial level. Serum transaminase and lactic dehydrogenase were normal. Figure 3 shows the liquefaction necrosis surrounded by neoplastic tissue occurring in the pons of this patient.

Cyst fluid removed at operation from a cerebral astrocytoma contained 20 times as much lactic dehydrogenase as transaminase activity. This difference was reduced to 2:1 in the cerebrospinal fluid of this patient (Table 3).

Pneumoencephalography.—Cerebrospinal fluid removed during air studies frequently contained enzyme levels which failed to correlate with the clinical diagnosis. The effect of pneumoencephalography upon cerebrospinal fluid enzyme activities was therefore investigated in eight patients. Ten-milliliter increments of spinal fluid removed prior to each air injection were analyzed for transaminase and lactic dehydrogenase activities, as well as cell content. Cerebrospinal fluid obtained by lumbar puncture 24 to 72 hours after the procedure was also studied. Two of the patients received no anesthesia or premedication.

In every case cerebrospinal fluid transaminase and lactic dehydrogenase activities increased rapidly to reach peak values by the end of the procedure. Levels reverted toward normal in 24 to 72 hours after the air study (Figs. 4 and 5). The rate of increase in enzymatic activity reached a maximum after the introduction of 30 cc. of air. The eventual levels reached appeared to correlate with the rapidity of the procedure. Cerebrospinal fluid cell counts did not increase during the air study but were

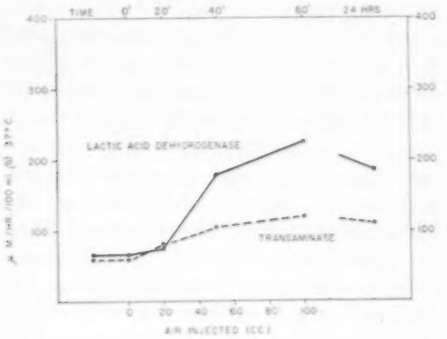

Fig. 4.—Changes in enzyme activity of CSF during pneumoencephalography. X-rays normal.

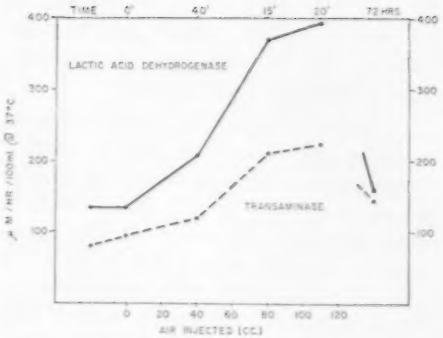

Fig. 5.—Changes in activity during pneumoencephalography. X-rays normal.

frequently high 24 to 72 hours later. There were no changes in serum enzyme activities.

Similar increases in cerebrospinal fluid enzyme activity occurred during ventriculography. The drainage of over 60 ml. of spinal fluid by lumbar puncture without air replacement did not result in a change of activity in one patient so studied.

Finally, the x-rays were interpreted as normal in all of these air studies.

Multiple Sclerosis.—Twenty cases of multiple sclerosis are included in this report. A careful history, complete examination by a competent neurologist, and a thorough cerebrospinal fluid study, including a γ-globulin determination, were obtained in each case. Doubtful, although probable, cases of multiple sclerosis were excluded. Patients, over 40 years of age, suffering a first attack of what appeared to be a demyelinating disease were not included in this series. In a few cases the major involvement was located in the spinal cord. Myelograms were normal, and in each instance the γ-globulin content of the spinal fluid was markedly elevated.

The cerebrospinal fluid transaminase activity was elevated in 11 of the 20 patients (Table 4). Three of these had 68μM of activity each, a borderline value. Increases were found either in active cases or in patients convalescent from a recent exacerbation. However, five patients with acute disease had normal levels. The average activity for all cases was 68μM, with a range of 31μM to 124μM. The mean for the 11 patients with elevated activities was 83μM, with a range of 68μM to 124μM.

The lactic dehydrogenase activity in the spinal fluid of the last 10 patients was determined and was elevated in 3 patients. These elevations averaged 109μM, an increase of 152% over the mean normal activity of this enzyme. In this same group the transaminase was increased in seven patients, averaging 89μM, a 200% increase above mean normal spinal fluid activity.

Comment

There is little to choose between cerebrospinal fluid transaminase and lactic dehydrogenase insofar as they reflect tissue damage in cerebral infarction. The data indicate that the dehydrogenase may be slightly superior in this respect, both in incidence of abnormality and in degree of increase. Both enzyme activities possess good clinical and pathologic correlations, as is evidenced by the high levels obtained in fatal cases. Especially to be noted are the

TABLE 4.—*Multiple Sclerosis*

Status	Transaminase, μM Mean	Transaminase, μM Range; Sample *	Lactic Dehydrogenase, μM Mean	Lactic Dehydrogenase, μM Range; Sample *
Acute	71	43–105; 15	77	62–102; 8
Remission	46	31–56; 4	62	(1 case)
Chronic	124	(1 case)	133	(1 case)
All cases	68	31–124; 20	81	62–133; 10

* Number of cases.

low spinal fluid transaminase activities of the patients who made excellent recoveries. However, enzyme levels occasionally have failed to correlate with outcome.

An examination of the values obtained in the series of verified central nervous system tumors reveals an interesting relation between transaminase and lactic dehydrogenase activities. Cerebrospinal fluid transaminase elevations were found in 10 of 24 cases, although these were appreciable in only 3. Lactic dehydrogenase activity was increased in the spinal fluid of all 11 patients where determined. The average transaminase increase over normal was 88%, as compared with the lactic dehydrogenase increase of 154%. Cyst fluid removed from an astrocytoma contained 20 times as much lactic dehydrogenase as transaminase activity. The relation of these enzymes in the spinal fluid of the tumor group contrasts with the nearly equal average increases observed in most cases of cerebral infarction. However, individual exceptions to this generalization have been common. A perusal of Table 3 reveals six cases of brain tumor in which the percentage increases of transaminase and lactic dehydrogenase were approximately equal. On the other hand, two cases of cerebral infarction have had normal transaminase and elevated lactic dehydrogenase activities. Thus the cerebrospinal fluid enzyme determinations were not of aid in the differential diagnosis of these eight patients.

The first 14 cases of brain tumor studied and reported elsewhere were all primary, and none were associated with elevated spinal fluid transaminase activity.[3] Toward the end of this previous survey the sensitivity of the methodology was increased by running all determinations at 37 C (made possible by a thermospacer accessory). This refinement may explain the slight elevations observed in an additional eight cases of primary brain tumor. It cannot account for the high value obtained in one case of metastatic carcinoma or for the elevated activities associated with two meningiomas.

The injection of air into the subarachnoid space produced striking elevations of spinal fluid transaminase and lactic dehydrogenase activities. This phenomenon was investigated by a clinical experiment in which the variables of serum activity, spinal fluid cell count, anesthesia and premedication, and presence or absence of central nervous system lesions were carefully followed. None of these correlated with the enzymatic changes. In addition, the experiment was repeated omitting air injection, with no resultant increase in spinal fluid enzymes. This eliminated the possibility that the phenomenon is due to sampling of fluid within the ventricles or cisterns.

No unusual complications of pneumography were present in any of the eight patients undergoing this procedure, and recovery was complete and prompt. It is difficult, therefore, to conceive of actual brain tissue destruction as the source of the increased enzyme activity. It must be assumed either that the meningeal and ependymal cells are broken down or that either these cells or parenchymal elements liberate enzymes under air irritation while preserving viability. If the latter explanation is conceded, the assumption that elevated cerebrospinal fluid or serum transaminase levels are always due to release of enzyme from necrotic tissue may be questioned. The evidence suggests that cells may release enzymes while retaining viability.

Substantial increases in cerebrospinal fluid transaminase activity were found in only 8 of 20 patients with multiple sclerosis. These increases were present in some, but not in all, of the acute cases and were absent in remission. There was no relation between the level and the anatomical or functional system involved in individual cases. The degree of severity or dissemination correlated with the spinal fluid transaminase activity only when the disease was acute. The transaminase activity proved superior to that of lactic dehydrogenase as an indicator of tissue damage due to multiple sclerosis, both in incidence and in de-

gree of elevation. Elevated cerebrospinal fluid transaminase and normal lactic dehydrogenase have not been encountered except in multiple sclerosis. The diagnostic value of this combination is greatly limited by its infrequency (4 of 11 cases).

While this paper was in preparation, Fleisher and his associates published a survey of transaminase and lactic dehydrogenase activities in the cerebrospinal fluid and serum of patients with neurologic diseases.[6] The results listed in their report are at variance with a large amount of the data included in this paper. The normal values for spinal fluid transaminase and lactic dehydrogenase obtained by these authors are aproximately twice those of our controls, 89.9 and 148.4 *vs.* 43 and 68, expressed in micromoles per hour per 100 ml. of CSF at 37 C. It is difficult to reconcile this difference, for Fleisher et al. did not describe their methodology in detail. In addition, there are few published reports on normal spinal fluid activities by other investigators. Bruns examined spinal fluid for lactic dehydrogenase but started reactions with spinal fluid, not pyruvate.[7] He found activities in general lower than those reported by Fleisher and colleagues. In the absence of other investigations of normal human spinal fluid transaminase activity, it is important to note that the relation of spinal fluid and serum activity in dogs found by Wakim and Fleisher is close to that reported by us for humans.[2] The transamination in the cerebral tissue of man and dog is very similar.[1,2]

The more frequent elevation of serum transaminase than of spinal fluid transaminase observed by Fleisher et al. in cerebral infarctions is contrary to our experience. Although we have not examined the serum of these patients routinely after an initial survey, we have encountered a few elevations which may have been due to central nervous system lesions. Significant heart disease is a frequent accompaniment of cerebral thrombosis or hemorrhage and may be responsible for occasional serum elevations noted by ourselves and others. The multiplicity of diseases which may increase serum transaminase activity detracts greatly from the value of serum determinations in the diagnosis of cerebrovascular disease. Evidence has been cited that serum levels as high as 37,000μM have relatively slight influence on the spinal fluid transaminase activity of patients free from significant neurologic disease. This impermeability of the blood-brain barrier therefore enhances the worth of the spinal fluid transaminase as an indicator of central nervous system lesions.

In a previous communication, we reported spinal fluid transaminase activity to be normal in patients having convulsive disorders not due to cerebral arteriosclerosis.[3] Fleisher et al. found several elevations among the epileptics they studied. They also indicated that all of these patients had pneumoencephalograms. If their results are based on the analysis of fluid removed during these procedures, the effect of the air injections alone could explain the increases of enzyme activities encountered by these investigators. The elevated activities they found in cases of cerebral atrophy and porencephaly could be similarly produced.

Summary

The destructive effects on the nervous system of cerebrovascular disease, neoplasms, and multiple sclerosis were accompanied by changes in glutamic-oxalacetic transaminase and lactic dehydrogenase activities in the cerebrospinal fluid. In general, both enzymes were elevated in the same incidence and proportions in cerebral infarctions. All central nervous system neoplasms studied, primary or metastatic, were associated with increased cerebrospinal fluid lactic dehydrogenase activity. Elevations of transaminase were neither as frequent nor as great as the lactic dehydrogenase changes in the tumor group. On the other hand, the transaminase activity proved to be a superior index of demyelination.

The value of these determinations in differential diagnosis is yet to be established because of common exceptions to these general patterns.

Department of Neurology, Georgetown University School of Medicine.

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Serum Aldolase in Muscular Dystrophies, Neuromuscular Disorders, and Wasting of Skeletal Muscle

LEWIS P. ROWLAND, M.D., and GEORGE ROSS, B.S., New York

In 1953 and 1954, the Schapiras, Dreyfus, and Kruh [8,9] reported that the concentration of serum aldolase was consistently elevated in patients with muscular dystrophy. Because of the potential importance of such a diagnostic test, we have attempted to evaluate this finding. While the present study was in progress, reports by Jacob and Neuhaus,[5] Aronson and Volk,[1] and Beckmann [2] appeared which confirmed the original description.

Methods and Material

Serum Aldolase.—The method employed for the determination of serum aldolase activity was essentially that of Sibley and Lehninger.[10,11] Only minor modifications were introduced. Sibley and Lehninger reported their results in terms of the number of cubic millimeters of hexose diphosphate substrate split per hour at 38 C (cu. mm. HDP/ml/hr.) in order to make their values comparable to the commonly used Q notation, in which Q (substrate) = (cubic millimeters of substrate acted upon)/(milligrams of dry tissue multiplied by the time, in hours) at 38 C. We feel that it is preferable from the points of view of the clinical chemist and the clinician to express the results in terms of the amount of triose phosphate (TP) in micromoles, formed by the enzyme per milliliter of serum per hour at 38 C; thus, one unit of aldolase is defined as that activity which will form 1 μM. of triose phosphate from hexose diphosphate per milliliter of serum per hour at 38 C at a pH of 8.6 (μM. TP/ml/hr.). In this paper the results will be given in both systems to facilitate comparison with work already published. To convert one system into the other, the expression 11.2 cu. mm. of hexose diphosphate = 1 μM. of triose phosphate [11] is used. In the method described by Sibley and Fleisher,[10] the triose phosphate was determined by coupling with 2,4-dinitrophenylhydrazine to form a chromogen of unknown structure which has an absorption maximum at 540 mμ. They then standardized the procedure by relating the optical density of the chromogen to the amount of triose phosphate, as determined by treating it with sodium hydroxide and measuring the inorganic phosphate liberated (the alkali-labile phosphate). We found it simpler and more direct to determine the triose phosphate by measuring the alkali-labile phosphate rather than by coupling with 2,4-dinitrophenylhydrazine. This procedure was used in the present study. After the splitting of the hexose diphosphate by the serum aldolase, the proteins were precipitated with trichloroacetic acid, and an aliquot of the filtrate was treated with NaOH to liberate the alkali-labile phosphate. The excess NaOH was then neutralized and the inorganic phosphate determined by the method of Fiske and Subbarow.[4] Appropriate corrections were made for the inorganic phosphate originally present in the hexose diphosphate * (which must be low) and in the serum. All determinations were carried out in duplicate. The differences between duplicates averaged about 10% of the higher value.

* A satisfactory grade of hexose diphosphate, as the barium salt, containing only traces of inorganic phosphate was obtained from Bios Laboratories, New York.

TABLE 1.—*Control Values for Serum Aldolase*

Category	No. of Subjects	Aldolase Activity: μM. TP /Hr/Ml.	S. D.	Cu. Mm. HDP /Hr/Ml.	S. D.
Normal subjects	45	0.55	±0.27	6.5	±3.1
Males	30	0.60	±0.27	6.7	±3.1
Females	15	0.55	±0.28	6.2	±3.0
"Nonwasted" patients	67	0.62	±0.27	7.0	±3.1
Total	112	0.62	±0.27	7.0	±3.1
Children less than 12 yr. old from both groups	18	0.72	±0.27	8.1	±3.1

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Miss Austra Pusplatais rendered technical assistance.

Post-Doctoral Fellow, National Multiple Sclerosis Society, Inc., (Dr. Rowland).

From the Division of Neurology and the Laboratory Division, Montefiore Hospital, and the Department of Neurology, Columbia University College of Physicians and Surgeons.

Subjects.—The subjects were divided into several groups. Controls consisted of 45 normal persons and 67 patients with disorders that were not characterized by muscular wasting, hepatitis, jaundice, hemolytic anemia, malignancy, or myocardial infarction. Included among the patients were 16 with epilepsy.

Patients with primary disease of muscle have been separated into several categories. Those with "pseudohypertrophic," facioscapulohumeral, and myotonic dystrophy have been diagnosed according to the usual criteria.[7,18] Adults included in the category of pseudohypertrophic muscular dystrophy had enlargement of the calves since childhood or, in one case, a history of this appearance in childhood. Patients with less clearly defined myopathies beginning before the age of 30 have been grouped as "limb-girdle" dystrophy,[18] a classification which

TABLE 2.—*Serum Aldolase in Patients with Various Types of Myopathies*

Patient	Age, Yr.	Sex	Duration of Symptoms, Yr.	Diagnosis	Aldolase Activity	
					μM. TP/Hr/Ml.	Cu. Mm. HDP/Hr/Ml.
				Pseudohypertrophic Muscular Dystrophy		
1	6	M	3		6.0	67.2
2	6	M	3		5.1	57.2
3	8	M	4		4.4	48.9
4	3	M	2		4.0	45.3
5	9	M	8		3.3	36.8
6	9	M	8		3.0	33.8
7	5	M	4		2.8	31.0
8	10	M	7		1.6	17.8
9	21	M	19		1.5	16.4
10	9	M	7		1.4	16.0
11	5	M	4		1.3	14.6
12	12	M	9		1.1	12.5
13	47	M	45 *		0.85	9.5
14	35	M	24		0.67	7.5
15	32	M	20		0.43	4.8
16	23	M	16		0.35	3.9
				Possible Pseudohypertrophic Muscular Dystrophy		
1	2	M	6/12		0.47	5.3
2	37	M	2		1.5	16.6
				Facioscapulohumeral Muscular Dystrophy		
1	35	M	Asymptomatic		1.0	11.7
2	42	F	20		1.0	11.6
3	31	F	7		1.1	11.8
4	41	M	25		0.34	3.8
				"Limb-Girdle" Muscular Dystrophy		
1	37	M	7		1.3	14.9
2	29	F	17		0.63	7.1
3	38	M	15		1.5	16.3
4	30	M	25		0.82	9.2
5	35	F	18		0.43	4.7
6	44	M	32		1.1	12.0
7	33	M	9		1.3	14.1
				Myotonic Muscular Dystrophy		
1	65	F	20		0.59	6.6
2	55	M	1		1.3	14.9
3	25	M	5		0.57	6.4
				Wasting Conditions of Uncertain Neural or Myopathic Origin		
1	51	M	3/12		1.0	11.6
2	67	M	1		0.80	9.0
3	65	M	35		0.57	6.4
4	55	M	20		0.51	5.7
5	33	F	17		1.4	15.2
				Polymyositis, Dermatomyositis, and "Nonspecific" Myopathies		
1	33	F	10/12	Dermatomyositis	0.54	6.1
2	14	F	1/12	Same	1.1	12.8
3	62	M	9/12	Same	1.0	11.0
4	56	F	1	Same	0.25	2.8
5	41	F	10	Polymyositis	0.53	6.0
6	55	M	3	Polymyositis with lupus erythematosus	1.2	13.1
7	49	M	6/12	Polymyositis with carcinoma	1.0	11.0
8	38	F	37	Myasthenic myopathy	0.65	7.4
9	72	F	1	Nonspecific myopathy with calcinosis circumscripta	0.85	9.5
10	55	F	3	Nonspecific myopathy	1.3	14.6
11	35	M	1	Nonspecific myopathy	0.94	10.5

* A photograph of this remarkable patient, taken in 1946, has been published [6]; the enlargement of his calves illustrated in that photograph has persisted.

is almost certainly heterogenous as to pathogenesis. Patients who have had histological evidence of inflammatory response in muscle biopsies at any time are classified as having "polymyositis" and are included in the group with "nonspecific myopathies" of later life. There was a small group of patients for whom no definite statement as to the origin of muscular wasting could be made even after detailed study, including muscle biopsy, electromyography, chronaxie determination, and examination of the cerebrospinal fluid. All but 10 of the patients with these various myopathies were examined and classified by one of us (L. P. R.). Most of the others were seen by Dr. Sidney Carter, pediatric neurologist of the Columbia-Presbyterian Medical Center.

In contrast to these patients is a group with "neural wasting," including 8 patients with amyotrophic lateral sclerosis, 5 patients with varieties of peroneal muscular atrophy (Charcot-Marie-Tooth disease), and 10 patients with various types of polyneuritis. In addition, studies were carried out on 11 patients with myasthenia gravis. Almost all of these patients were also seen personally.

Results

The values for serum aldolase activity in normal persons and in patients used as controls are given in Table 1. There was little difference between the normal male and the normal female subjects; the mean value for the larger group of "nonwasted" controls was only slightly higher. The value for children selected from both these groups was slightly higher than that for the adults. Although the mean normal value of 0.58μM. TP/ml/hr. (or 6.5 cu. mm. HDP/ml/hr.) is quite similar to that reported by others, our standard deviation is somewhat larger, and the upper limit of normal of 1.4μM. TP/ml/hr. (or 16.0 cu. mm. HDP/ml/hr.) (approximately three times the standard deviation) is somewhat higher than that given by the original authors.[10]

The values for serum aldolase activity in patients with muscular dystrophies, other wasting conditions, and myasthenia gravis are set forth in Tables 2 and 3. Significant elevations occurred only among patients with the pseudohypertrophic form of muscular dystrophy. In occasional instances borderline values were found among patients in other categories.

TABLE 3.—*Serum Aldolase Values in Nonmyopathic Conditions Characterized by Muscular Wasting and Other Neuromuscular Disorders*

Diagnosis	Units of Aldolase Activity *
Neural wasting	
Amyotrophic lateral sclerosis	0.51 (5.7), 0.54 (6.0), 0.70 (7.8), 0.76 (8.5), 0.79 (8.9), 0.93 (10.3), 0.93 (10.3), 0.96 (10.8)
Polyneuritis	0.30 (3.4), 0.33 (3.7), 0.36 (4.0), 0.40, (4.5), 0.73 (8.1), 0.75 (8.4), 0.76 (8.5), .0.77 (8.6), 0.87 (9.7), (1.60 † 18.0)
Peroneal muscular atrophy	0.30 (3.4(, 0.48 (5.4) 0.62 (7.0), 0.74 (8.3), 1.2 (13.6)
Syringomyelia	0.89 (10.0), 1.0 (11.4)
"Amyotonia congenita"	1.2 (12.9), 1.5 (16.3)
Radicular lesions	0.37 (4.1), 0.59 (6.6)
Severe malnutrition	
Anorexia nervosa	0.30 (3.4), 0.50 (5.6)
Bilateral carotid artery thrombosis	1.5 (16.3)
Multiple sclerosis	0.46 (5.1)
Hepatolenticular degeneration	0.80 (8.9)
Wasting associated with paraplegia or quadriplegia	
Multiple sclerosis	0.41 (4.6), 0.44 (4.9), 0.80 (9.0), 0.82 (9.1), 1.3 (14.7)
Myelopathies of uncertain cause	0.38 (4.2) 0.48 (5.4) 0.60 (6.7) 1.1 (12.8)
Compression myelopathy	0.97 (10.9), 1.0 (11.2)
Malignant disease	
Carcinoma	0.38 (4.2), 0.39 (4.3), 0.59 (6.6), 0.60 (6.7), 0.61 (6.8), 0.62 (7.0), 0.65 (7.3), 0.67 (7.5), 0.78 (8.7)
Myelomatosis	0.48 (5.4), 0.52 (5.9), 0.56 (6.3)
Neuromuscular disorders	
Myasthenia gravis	0.29 (3.3), 0.44 (4.9), 0.49 (5.5) 0.57 (6.4), 0.57 (6.4), 0.61 (6.9), 0.65 (7.3), 0.68 (7.6), 0.73 (8.2), 0.77 (8.7), 0.84 (9.4)
Periodic paralysis	0.62 (7.0)

* Each pair of figures represents the aldolase value for an individual patient. The first figure of each pair represents units expressed as micromoles of triose phosphate per hour per milliliter (μM. TP/hr/ml.); the figures in parentheses, the units expressed as cubic millimeters of hexose diphosphate per hour per milliliter (μM. HDP/hr/ml.).

† This patient also had leukemia.

Comment

In this study, the level of serum aldolase activity proved to have limited value as a diagnostic aid. Elevations were found only in patients with pseudohypertrophic muscular dystrophy, but this is the form which offers the least difficulty diagnostically because of its characteristic clinical features. Furthermore, even in indisputable cases in an active stage of the disease, the aldolase value might be normal.

Nor did the level of aldolase activity assist in the diagnosis of the other myopathic disorders, which have to be distin-

guished from wasting conditions secondary to disease of the motor neuron or peripheral nerve. It also failed to assist in the separation of the various "limb-girdle" and "nonspecific" myopathies into categories more meaningful than is permitted by presently available clinical and histological criteria. Serum aldolase values were normal in all such patients in the present study. In other reports [1,3,14] some patients with myopathies of adult life have had slightly elevated serum aldolase activity, but so also have some patients with wasting secondary to denervation.[1]

However, the striking elevations seen in patients with muscular dystrophy pose an interesting problem. It is evident from the data given in Table 2 that the definite elevations were seen only in young children, whereas patients who had survived the disease into adult life had normal values. This occurrence has also been noticed in other studies [1,11] and suggests that the aldolase level may have some value as an index of activity of the disease process.

Regardless of the ultimate practicality of serum aldolase values as a diagnostic or prognostic adjunct, it will be important to ascertain the cause of the distinct elevations in pseudohypertrophic muscular dystrophy. The chronic nature of this condition makes it unique among diseases which have been found to be associated with elevation of serum enzyme activity, almost all of which are acute. The prominence of acute tissue necrosis in diseases characterized by elevated transaminase activity has led to the suggestion that tissue enzymes are released into the blood as a consequence of the local injury.

Analogous reasoning may apply to muscular dystrophy because Dreyfus and the Schapiras [3] have shown that concomitant with the elevation of serum aldolase activity, there is a diminution of aldolase activity in the muscle. The possibility, therefore, exists that alterations in cellular permeability of the diseased muscle permit the escape of tissue proteins into the serum, including not only aldolase but also transaminase.[12,14,15] However, one might then expect elevation of enzymatic activity in the other myopathies as well, and perhaps also in those conditions grouped as "neural wasting," since some of the subjects were also in an apparently active phase of the disease. We did not find elevated aldolase activity in these conditions or in apparently active cases of dermatomyositis, although Siekert and Fleisher [12] and White [14] found transaminase elevated in dermatomyositis. White also found both lactic dehydrogenase and aldolase activity to be enhanced in dermatomyositis. Another possible explanation for the elevation of enzymatic activity in the blood is that there is a nonspecific change in the production or degradation of these serum enzymes, the normal mechanisms of which are not known at present.

Summary

Of 16 patients with pseudohypertrophic muscular dystrophy, 10 showed significant elevations of serum aldolase activity. Several of the normal values were obtained in older patients who had survived many years of the disease, and it is possible that the aldolase level may serve as an index of activity of the disease. However, some young patients, apparently still in an active phase of the disease, also had normal values.

Patients with facioscapulohumeral muscular dystrophy, "limb-girdle" dystrophy, myotonic dystrophy, polymyositis, dermatomyositis, and nonspecific myopathies had normal values. Normal values were also found in patients with muscular wasting due to disease of the motor neuron or peripheral nerve, in wasting conditions due to malnutrition, and in myasthenia gravis.

Neurological Institute, 710 W. 168th St. (32).

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Pelizaeus-Merzbacher Disease

A Clinical Study

H. RICHARD TYLER, M.D., Boston

In 1885 Pelizaeus [1] described a family affected by a slowly progressive hereditary form of cerebral diplegia characterized by the early development of nystagmus, ataxia, and spasticity. Merzbacher,[2] in 1907, examined pathologically a brain from a relative of the same family who had suffered from the illness which Pelizaeus described. Spielmeyer,[3] in 1913, and Liebers,[4] in 1928, studied another brain from this family. There have been isolated reports of individual cases and families in which a similar neurological disorder has been found, but the family reported by Pelizaeus and Merzbacher has been the only one in which the disease has extended back over a number of generations. My associates and I have recently encountered another large family that we feel is worth while recording because of its size and similarity to that of the original report. The time of onset and the symptomatology, as well as the course of the illness, are the same as in Pelizaeus' original family. The following seem to be the only points of difference in the two families: The pattern of onset of symptoms in our group appeared more rigid; none of our female members were affected (2 out of 14 in the Pelizaeus-Merzbacher family were involved), and, perhaps, remissions were not as obvious in our cases.

Presentation of Cases

CASE VI-78, a 16-year-old Negro youth. The mother had a normal pregnancy. The delivery, after an easy labor, was uncomplicated, and no instruments were used. The child breathed spontaneously, and physical examination at the time of birth was normal. Eight to ten days after birth the mother noted that the baby's eyes began to "roll" and that he "tossed" his head from side to side. Physical examination at the time revealed an intermittent nodding and side-to-side tremor of the head of rapid rhythm (80 to 100 times a minute). It was noted to persist for a few minutes and then stop, only to begin again. The movements were characterized as forceful, and amplitude of the head excursion was "fairly big." The fontanels were described as normal. There was a coarse, constant nystagmus, mostly to the left, with a rotatory component. There was a suggestion of athetoid movements in the arms. During sleep all movements disappeared. There were no cerebellar signs. The baby's legs were noted to be slightly spastic with active knee jerks, but neither ankle clonus nor paralysis was noted. He remained unchanged until 7 months of age, when it was noted that he would keep his thighs adducted and flexed at the hips and knees. At 2 years of age he was unable to walk, though it was felt he had good muscle power in his legs. His head could not be supported and would fall back when he was lifted. He made no attempt to sit. According to his parents, his vocabulary was limited to two or three meaningful words. They also felt that the child's legs were becoming weaker. A physician who saw the child at that time noted kyphoscoliosis, flaccid paralysis of the legs with atrophy, and hyperactive deep reflexes. At 2½ years of age the patient had a performance equivalent to a mental age of 3 months. He had not learned to crawl or stand. He remained unchanged until he was admitted to Wrentham State School, Wrentham, Mass., at the age of 7 years. Here it was observed that he had not developed any further, and had probably lost a little ground. It was noted in the hospital record there that he could make grunting noises, but did not talk. He had marked nystagmus in all directions of gaze. Vision and hearing were felt to be normal. There were adductor spasms of the legs and hyperactive reflexes. Objects were grasped, with poorly controlled movements. The

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Howard Hughes Medical Investigator.

From the Neurological Unit of the Boston City Hospital, the Department of Neurology, Harvard Medical School, and the Pearl Memorial Unit, Peter Bent Brigham Hospital.

head was balanced with difficulty. Incontinence of urine and feces was present. He remained the same until he was transferred to the Neurological Unit of the Boston City Hospital for further investigation, at the age of 16.

The past history and system review were noncontributory.

On admission, the blood pressure was 120/70, pulse 86 per minute, temperature 99 F, and respirations 20 per minute.

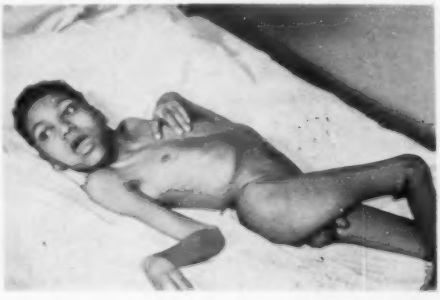
The patient was a poorly developed, well-nourished Negro youth, in no acute distress. He was of small stature. When in bed, he lay with his legs drawn up, eyes and mouth open, face emotionless. He hummed to himself and made grunting noises. The head was 19.4 in. in circumference. His palate showed a very high arch. There was no pubic or axillary hair. The genitalia were normal. There was a marked kyphoscoliosis to the left. The heart was normal, and the chest was clear. The liver and spleen were not felt. Both ankles were lax, the feet being everted and plantar flexed. His visual fields, judged by confrontation with objects, seemed full. The patient would follow objects moved in his field of vision. The discs were paler than normal, with deep physiological cups. The vessels, retina, and macula were normal. The pupils were round and equal and reacted to light briskly. The extraocular movements were full. There were a pendular nystagmus on forward gaze and a jerkier horizontal and rotatory nystagmus on lateral gaze. This jerky movement of the eyes was also present on central fixation. The corneal reflexes were present, and masseter muscles were normal. There was no facial paralysis; hearing and swallowing were intact. The patient seemed to have great difficulty in supporting his head. When he was lifted up, his head fell back, with weak flexion movements of his neck. There were slow grimacing movements of the face, and a tremor was present in the jaw. The tremor was of small amplitude and of about 2-3-per-second frequency. Both hands showed slow movements of hyperextension and flexion with pronation and supination of the forearm characteristic of athetosis. The thumb was frequently caught between the first and second fingers. There were occasional movements of the shoulder, abduction-adduction in type. He reached for objects in a wavering, slow, nonrhythmical way. He made clumsy attempts to brush things away with his hands. The legs were usually crossed. All muscles of the upper extremity were small. The quadriceps muscles were smaller than the hamstrings, and there was hardly any muscle palpable in the anterior tibial compartment of the legs. Flexor spasms were present. Spasticity was present in the legs and, to a less extent, in the arms. There was marked hypotonia at the wrist, fingers, and ankle. Deep tendon reflexes were brisk, with bilateral knee and ankle clonus and bilateral extensor plantar responses. There were no abdominal reflexes. He was incontinent of urine and feces. He responded to noxious stimuli in all parts. Further sensory testing could not be evaluated. There was no readjustment of body posture when the patient was supported in a horizontal plane and the head flexed and extended. He had no placing reactions and could not turn himself over.

Laboratory data revealed a hematocrit of 44%, with a hemoglobin content of 12.0 gm. per 100 cc. The red blood cells looked hypochromic and normocytic. The white blood cell and differential counts were normal. Urinalysis revealed no abnormalities. Spinal fluid examination showed an initial pressure of 110 mm. and a final pressure of 60 mm. There were no cells, and the protein was 22 mg.%. The colloidal gold curve was 1122210000. Tests for phenylpyruvia and sickling were negative. The blood Hinton test was negative.

Figure 1 shows the patient in a characteristic posture.

CASE VI-80, a 9-year-old Negro boy. He was born 20 days prematurely after a pregnancy that was otherwise normal. Physical examination at the time of birth was completely normal. There was no nystagmus, and the Moro reflex was present. Eight days after birth his mother noted that his eyes "rolled" like those of his older brother. He was examined at a neurological clinic at one month of age, when the finding of nystagmus was confirmed. The child's development advanced somewhat more than that of his older brother. He was able to pull himself up and crawl by the age of 2 years, but the use of his legs always remained poor. By this time a tremor of the head had been noted. The parents said he was able to say a few words. He remained essentially unchanged until the age of 5 years, when he was noted to reach out for things. He had difficulty in holding his head erect. The muscles of his arms, legs, and

Fig. 1.—A typical posture of Case VI-78. Notice the open mouth, kyphoscoliosis, and small muscles of the extremities. The hand postures reflect the hypotonia noted in this patient.



thighs were noted to be very small. He could move all his extremities, though imperfectly, and his arms better than his legs. He was admitted to the Wrentham State School, where a further report, when he was 8 years old, was as follows: "His head and hands seem to be in constant motion. Both legs are in tight extension. He can crawl around the floor. He appreciates attention but has a short attention span. He has a coarse nodding tremor of the head. The lower limbs show severe muscular atrophy with slight extensor contractures. There is a horizontal nystagmus. There is ataxia on intention use of the hands. The legs show adductor spasms and scissoring. Reflexes are increased, with increased muscle tone. He has a strong grip. His mental age is about 7 months."

The patient remained essentially the same during his hospitalization and was transferred to the Neurological Unit of the Boston City Hospital for further investigation at the age of 9. No further data regarding the past history and system review were obtained.

Physical examination revealed a well-developed, well-nourished Negro boy in no acute distress. The blood pressure was 110/70, pulse 90 per minute, respirations 23 per minute, and temperature 98.6 F. The head measured 19.5 in. in circumference. The occipital bone appeared flattened. On examination the ears, nose, and throat appeared normal. There was severe kyphoscoliosis. The chest was clear and the heart normal. The liver and spleen were not palpable. The genitalia were normal. He would lie quietly in bed all day long. He had no vocabulary but could make sounds. He could see and be encouraged to reach for objects. The optic discs were paler than normal. The retina and macula were normal. No facial paralysis or difficulty in swallowing was noted. His hearing was intact. This patient had marked thinning of all the muscles of his arms and legs, with obvious hypotonia. His legs never moved spontaneously, except for occasional flexor spasms. He had athetosis of the hands and grimacing of the face, with abnormal athetoid lip and tongue movements. There was a 1-2-per-second horizontal tremor of the head, irregular in amplitude, especially noted in the sitting position. There was no change in body posture when the head was flexed or extended on the body and the patient supported in a horizontal plane (neck-righting reflex). He had no tonic reflexes or placing reaction. The reflexes were hyperactive, with ankle clonus and extensor plantars. There was no demonstrable sensory loss to pinprick. Vibration, touch, and position sense could not be adequately evaluated. The patient was incontinent of urine and feces.

Laboratory data revealed a hemoglobin of 10.5 gm. per 100 cc. and a red blood count of 3,950,000 cells per cubic millimeter, with hypochromic normocytes. Urinalysis was negative. A spinal fluid examination showed an initial pressure of 170 mm. and a final pressure of 130 mm. There were no cells, and the protein was 32 mg.%. Tests for phenylpyruvia and sickling were normal. Blood and cerebrospinal fluid Hinton tests were negative.

Case VI-88, a 16-year-old Negro boy. The mother reported that she had had a normal pregnancy, except for an upper respiratory infection during the third month of gestation. Labor lasted 3 hours and 45 minutes. The infant, delivered by instruments from a vertex presentation, did not breathe for several minutes, when respiration started spontaneously. The umbilical cord was coiled around his neck, but did not seem to be compressing his throat. He was noted to have normal Moro reflexes and no paralysis at the time of birth. The eyes were noted to be normal. He was placed in an oxygen tent for 36 hours. When the mother first saw him (at 36 hours), she noted he had several petechiae on the face, but seemed otherwise normal. At the age of 3 weeks he was noted by his mother to have regular, rhythmical movements of the eyes, which decreased slightly and seemed least obvious when the patient looked at an object. When he was 6 months old, the mother noted head movements similar to those of his two older brothers, but much less marked. He was unable to hold up his head until 13 months of age; however, in the months prior to admission he had been able to turn from his stomach to his back, but not vice versa. He usually lay on his back with arms flexed and legs in a frog-like position at the hips with external rotation, and flexion at the knees. In the previous few months the nodding tremor of the head had become more obvious. He followed objects with his eyes and could say two words. He could hear well, and would play with his hands and feet.

The past history and system review were completely noncontributory.

Physical examination revealed a well-developed, well-nourished child in no distress. The blood pressure was 100/60, pulse 100 per minute, respiration 18 per minute, and temperature 98.6 F. The head measured 18 in. in circumference. The fontanels were closed. The occipital portion of the skull was very flat. No bruit was heard. The eyes, ears, nose, and throat were all normal. There were a few shotty axillary lymph nodes. The chest was clear to sinus tachycardia, with a Grade 1 apical systolic murmur. The liver and spleen were not palpable. The genitalia were normal.

The child reached for objects, but did not reach for things he dropped. He was content to lie quietly in bed all day. Fundus examination revealed slightly pale discs, but the macula and retina were normal. The pupils were round and regular and reacted briskly to light. There was a pendular

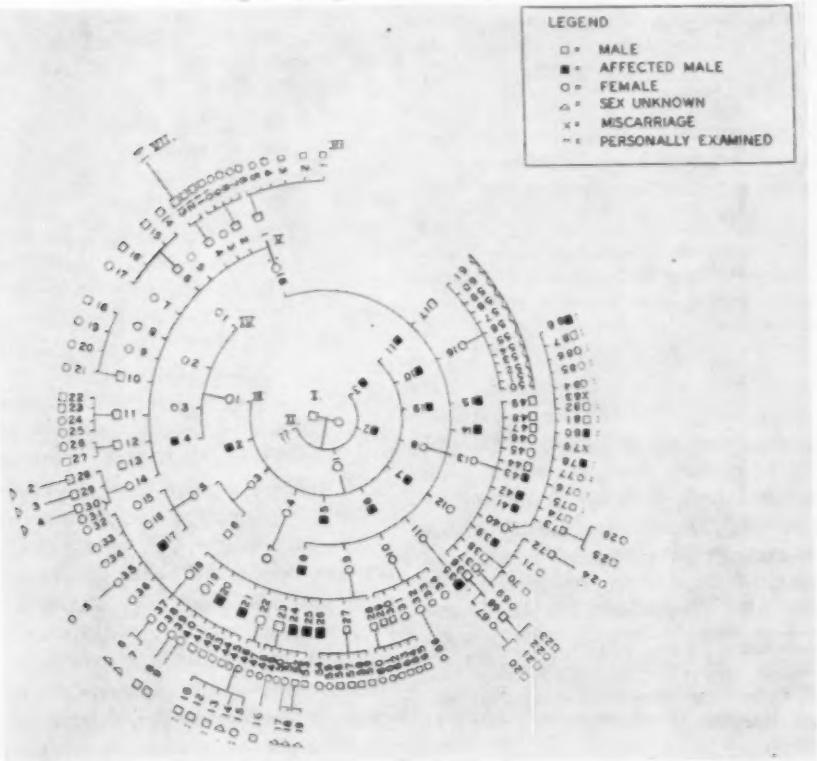
nystagmus, which became jerkier on lateral gaze but did not disappear when the patient fixated. There was a full range of extraocular movements. The corneal reflexes were present. There was no weakness of muscles supplied by the seventh nerve, and hearing was intact. A normal gag reflex was present. The child could not support his head alone. There were no neck-righting reflexes. Tonic neck reflexes were only partially present. The Landau reflex was normal. There was a slow 2-3-per-second tremor of the head, of flexion-extension type and irregular in amplitude. Rarely, a side-to-side component was noted. There was also a tremor of the jaw of the same character. There were some grimacing movements of the face. The hands showed obvious athetosis with pronation-supination movements at the wrist and hyperextension-flexion of the hands, with many quick movements of the fingers. The legs showed some athetoid movements. There were a generalized hypotonia of the distal parts of the extremities and an obvious weakness of the legs and thighs. There were no placing reactions. The legs were often drawn up in flexor spasms. The child could turn over when placed on his stomach, which he did mainly by trunk movements. He could not sit up. The reflexes were equal and hyperactive. There was sustained knee and ankle clonus bilaterally with bilateral extensor plantar responses. He responded to pinprick everywhere. It was impossible to evaluate sensory testing any more accurately.

Laboratory data revealed a hematocrit of 36% and a hemoglobin of 10.5 gm. per 100 cc., with 5,400,000 red blood cells. These appeared normocytic and hypochromic. Tests for iron in the blood showed a level of saturated iron of 63μg. per 100 cc. This demonstrated that the anemia was due to iron deficiency and did not have a hereditary basis. The urinalysis was normal. Spinal fluid examination showed an intitial pressure of 130 mm. and a final pressure of 120 mm. There were no cells, and the protein was 40 mg.%. A colloidal gold curve was 0000000000. Blood and cerebrospinal fluid Hinton tests were negative.

Other Data

Electroencephalograms were taken on all three patients. They revealed only a slight excess of slow 5-6-per-second activity in all the records. This was

Fig. 2.—Pedigree of the family reported.



regarded as a nonspecific change that was nonfocal and nonparoxysmal.

X-rays were taken of the skulls, vertebrae, and long bones. The skull films showed some shortening of the middle fossa in all three patients and flattening of the occipital bone. This was thought to be due to prolonged recumbency of a retarded child with secondary changes in skull shape, such as is so commonly seen in defective children. The vertebrae were normal, but the films showed the kyphoscoliosis that was noted clinically in two of the patients. The long bones were very thin, but the cortex and trabecular pattern were normal. These changes were felt to be nonspecific.

Nine siblings and twelve relatives were examined, and no evidence of an abortive form of the disease was found.

Figure 2 is a chart of the pedigree of this family through seven generations. There have been at least 27 members (all male) who have suffered from the same illness.* It can be seen that the disease was transmitted by female members of the family.

None of the affected males had any progeny. Unaffected males never passed the disease to their offspring. Details of affected members are given in the "Appendix."

There has been only one postmortem study in this family. The patient, a first cousin of the mother of the three patients reported here, died in 1927 in a mental hospital at the age of 27. Records from the hospital and an interview with the pathologist who was at the hospital at the time of examination produced only the following data: "The brain was removed from the cranial cavity, and an excess amount of cerebrospinal fluid was noted over the convexity. The brain was small and heavy. The sulci were prominent; the gyri were grossly normal. There was no gross malformation. The brain was sliced serially and no gross abnormality was noted." Unfortunately, the brain was then destroyed, and no microscopic sections were made.

Comment

The family examined by us is notable in that 27 members in seven generations were affected in a fairly stereotyped and predictable manner. The disease was always transmitted through an unaffected female, and the affected male never reproduced. No instance of a female with the illness was known. If the male was not affected, then his children, including the daughters, did not reproduce the disease. About one-half of the females had affected children. The disease was recognized to be in the family for many "generations," but only definitely known cases are included in this report. The children were known to other members of the family as "head nodders" and "eye waggers." The condition was usually first observed about 8 to 10 days after birth, and sometimes as late as 3 months. The parents noted that the eyes were constantly moving and that the head was moving in a repetitive side-to-side tremor. The children were hypotonic and rarely learned to sit or stand, but in some cases development reached the stage where the head could be held up, aberrant attempts to crawl were made, and a word or two could be said. Placing reactions were usually lost by 18 months of age. Some of the patients could propel themselves by a peculiar writhing-snakelike motion of the body with head held extended. This was the only demonstration of a righting reflex noted. By the age of 3 to 6 years, kyphoscoliosis, spasticity in the lower extremities, athetosis, intention tremor, and slight regression in the mental state were noted. The upper limbs became slightly spastic by the age of 10 to 12 years. The rate of progression of the disease seemed to become slower and slower with each year until it appeared almost as though in some of the older affected persons the disease eventually became stationary. Thin arms and legs were noted in some members of this family. Most of the patients died of intercurrent infection in early years. One lived to 51 years of age.

The predominance of brain stem signs, except for nystagmus, in these patients has not been emphasized in the literature. The early onset of nystagmus, ataxia, defects in posture and placing reactions, and disorders in the major righting reflexes are all prominent in the examination of the patient with Pelizaeus-Merzbacher disease; indeed, at the early stage, these signs con-

* Since this paper was submitted, another male child, sibling of one here reported, has been born and has shown unequivocal signs of being similarly afflicted. He would be represented on Figure 2 as VI-89.

stitute the major abnormal neurological findings. This is in contrast to the patients who present first with focal cerebral symptomatology, as is usual in familial and sporadic cases of diffuse sclerosis and metachromatic leukoencephalopathy. This would seem a useful clinical point in differentiating these diseases.

Pelizaeus [1] described a family in which the children were born normal, nystagmus and head movements developing at 3 months of age. Those abnormal movements sometimes disappeared. By the age of 2 years there was spasticity and incoordination, first appearing in the lower extremities. The reflexes were increased, and the patient had difficulty in walking. At about 6 years of age, paresis of the lower extremities, contractures, psychic changes, mental deterioration, staring facial expression, and athetosis all became noticeable. The youngest patient was 1 to 2 months of age; the oldest was 28 (and died later, at the age of 52). There was some variation in time of onset and rate of progression.

Merzbacher [2] reported on the same family as did Pelizaeus and added six affected members to the family history. He was able to study the brain of one patient of the family, and this showed a diffuse symmetrical atrophy of white matter, which seemed to originate at the ventricular surface and spread peripherally. The myelin sheaths were severely affected, with little islands of sparing, which he called *Markinseln*. The cortex and subcortical fibers were intact. The cerebellum was diminished in size, and the brain stem was small and "bluish" in color. The latter was not examined histologically. Merzbacher felt that he was dealing with a congenital maldevelopment and applied the name "Aplasia axiales extra-corticales congenita" to the condition.

The similarity between the Pelizaeus-Merzbacher family and the family we are reporting is indeed impressive in terms of onset, type of symptoms, and signs. Age of onset, order of appearance of signs, and the striking chronicity of the ailment were all identical in the members affected.

Spielmeyer [3] studied the brain of another patient (a sister of Merzbacher's patient) and noted that, in addition, the brain stem, pons, medulla, and spinal cord were severely affected. There was extensive demyelination in all these areas, as well as the cerebellum and cerebrum. The fourth ventricle was noted to be large. There was a decreased number of olivocerebellar fibers, and the olive was degenerated bilaterally. He felt there were some gray-matter lesions (foci of neuroglial proliferation with fat globules) in the cortex, medulla oblongata, and spinal cord as well. Both he and Liebers,[4] who later studied the same brain, felt the disease was more likely to be degenerative than developmental.

There are only a few other cases with similar heredofamilial incidence. Pesker [14] reported on two brothers who had a diffuse sclerosis, and whose two maternal uncles had a "paralysis." Böstrum [5] reported on five brothers and one cousin, with clinical and pathological studies. Merzbacher [2] reported another family with four brothers affected, one maternal uncle having had the same disease. Scholz [6] described a family of three siblings who gave a two-year history of nystagmus, followed by cortical blindness, receptive aphasia, and cortical deafness. The onset had been between the ages of 8 and 10 years. Later, spastic ataxia of the legs, dementia, and pseudobulbar phenomena became marked. In these cases pathological examination revealed that the brain stem was severely affected. Two grandfathers (who were brothers) had a neurological disease at the age of 29 or 30 that probably was a hereditary spastic paraplegia. There were no remissions. Walthard [7] and later, Pfister [8] added another case to Scholz' family and described the family further. Their case was important in that the pathological study showed that the white matter of the cerebellum was severely affected, in contrast

to the cases earlier described by Scholz. Scheftel[9] reported on two brothers, with a cousin similarly affected. Meyer and Tennent[10] reported on two brothers who had diffuse sclerosis, which appeared at the age of 18, and whose mother later became ill with what was probably multiple sclerosis. Einarson and Neel,[11] Curtius,[12] and Bielschowsky and Henneberg[13] described familial cases of diffuse sclerosis with an ancestral history of hereditary spastic paraplegia.

It is obvious from the reported pathology that Pelizaeus-Merzbacher disease has many points of resemblance to diffuse sclerosis. It seems now generally accepted that this disease represents a clinical variation or subdivision of diffuse sclerosis. The early onset of symptoms, often in the first weeks of life, the exceedingly chronic course of the disease, and its heredofamilial nature have been the characteristic features usually mentioned in discussions attempting to separate the disease from the other leukoencephalopathies. To this we would add the predominance of signs related to the brain stem that appear early in the course of the illness.

We shall have to await postmortem verification of the pathology in our cases; but, in the interim, we feel it worth while to report this family in order to bring to the attention of the clinician and the geneticist another example of a rare and interesting hereditary disease.

Summary

A clinical report of a disease affecting at least 27 members of a family in seven generations is presented. The symptomatology is that of diffuse sclerosis of the subcortical white matter, as first described by Pelizaeus and Merzbacher.

The early development of nystagmus and other brain-stem signs distinguishes the illness from the familial forms of Schilder's disease (progressive subcortical encephalopathy) and metachromatic leukoencephalopathy.

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Appendix

Data concerning the affected members shown in Figure 2 are as follows:

II-2 and *II-3: IV-18* was told by grandmother (II-1) that she had "many" brothers who had the disease and that it had run through the family for many generations on the mother's side.

III-2, III-5, III-6, III-7, III-9, III-10, III-11: *IV-18* was told by *III-8* that she had seven brothers who had the same trouble that was known to run in the family. She said: "They were normal at birth but later developed eye and head movements. They never could walk."

IV-4: Known to have lived to age of 31. "Never could walk or talk. His eyes jiggled. He had the disease" (quoting *V-22*).

IV-8, IV-14: Both described by *IV-18* and *V-22* as typically affected with eye movements, and paralysis of the legs.

IV-15: Died at age 51. "He was crippled like his brothers. He never could talk, and his eyes moved like all the others" (quoting *IV-18* and *V-22*).

V-17: Died at age of 41 with typical disease. He was never able to walk, but spoke in a manner that only the family could understand. He had typical eye movements. He was always a bedridden person, and was known to be incontinent of urine and feces.

V-20: Died at age of one with typical disease" (*V-22*).

V-21: Died at about 3 years of age. "He had the same eye movements as his brothers. His head nodded. He was also very loose-jointed. He never learned to walk" (quoting *V-22*).

V-24: Died in infancy. He had the typical disease, according to *IV-18* and *V-22*.

V-25: Died at age of 28. "He had the eye movements and couldn't use his legs. He was always an invalid, was unable to walk or talk, but grew to be 6 ft. tall. The last few years of his life he had to be fed by a tube." He was noted to be hypotonic and was described by one physician as follows: "A bedridden Negro idiot who has been crippled since birth. There is atrophy of legs and feet. They are very weak. He is unable to walk or talk. The legs are drawn up in adductor position. Pupils are equal and react to light sluggishly." The patient died of pneumonia about 20 years ago. Autopsy was performed, details of which are reported in this paper.

V-26: Said to be typically affected (quoting *V-22*).

V-35: Died in infancy, affected, according to *V-22*.

V-39: Died at age 3 years; "shook head, and eyes" (quoting *V-22*).

V-41: Died at age 3 years, of measles; said to be affected (*by V-22*).

V-42: Died at age 11 years of pneumonia; "his head and eyes moved; he never talked and could not walk" (*V-22* and *IV-18*).

V-43: Living at age of 41; "we think he is very smart. He has long thin legs. His legs frequently jump and then draw up. His speech is very difficult to understand unless you've been around him for years. He cannot feed himself because of unsteady hands, but he can get a cookie to his mouth occasionally. He shakes a lot. He has no control of his bowels."

VI-78, VI-80, VI-88: Details are given under the case presentations.

Department of Neurology, Harvard Medical School.

Intracranial Hemorrhage in Cerebral Arteriovenous Anomalies

MATTHEW W. WOOD, M.D., and HENDRIK J. SVIEN, M.D., Rochester, Minn.

The significance of intracranial bleeding from ruptured aneurysm is well appreciated. The high mortality rate resulting from such intracranial catastrophies has been reported in detail by Hamby,[1] Wolf and associates,[2] Magee,[3] and others. Although figures from these various authors differ to some extent, an approximation arrived at by Williams and co-workers[4] in a recent paper perhaps expresses the experiences of most students of the subject. These authors found that approximately one-third of the patients with subarachnoid hemorrhage resulting from cerebral aneurysm died within the first 48 hours, another third died in the following 12 days, and a sixth died within the remainder of the first 4 weeks. The remaining sixth survived longer than four weeks. On the other hand, Logue[5] reported a mortality rate of 13.5% for surgically treated patients with these lesions, against a rate of 44.4% for a control group of patients who were treated nonsurgically. So we see that the prohibitive mortality rate associated with the nonoperative management of cerebral aneurysm makes early surgical intervention something to be considered very seriously.

In sharp contrast to these exhaustive studies on aneurysm is the paucity of reports in the literature on the long-term follow-up of bleeding arteriovenous malformations. This is due mainly to the relative infrequency of arteriovenous anomalies as compared with aneurysms, the former comprising only about 1% of brain tumors. The scanty literature that is available on the subject is somewhat confusing and in part conflicting.

Dandy,[6] in reporting on 8 of his own cases and on 22 collected from the literature, concluded that about 40% of untreated patients with arteriovenous anomalies die of cerebral hemorrhage. Olivecrona and Riives[7] found that in almost half of their cases of arteriovenous anomaly there was a history of one or more hemorrhages with hemiplegia, which was usually transient. They stated that in the end, probably most, if not all, patients with this type of lesion die of hemorrhage or are completely incapacitated. Gould and co-workers[8] had a mortality rate of 20% from hemorrhage for their entire series. Mackenzie[9] recorded 26 instances of subarachnoid bleeding in 50 cases of arteriovenous anomaly. He expressed the view that the mortality rate due to hemorrhage from such lesions is substantially less than that from aneurysms. Other authors support this view. In 1951 Bassett[10] reported on 18 patients, of whom 11 had subarachnoid hemorrhage, but he went on to state that the effect of such hemorrhage was not as devastating as that from the subarachnoid or intracerebral hemorrhage accompanying rupture of an aneurysm. He further stated that these patients suffer from frequent recurrent hemorrhages, but felt that they were rarely fatal. Gillingham[11] reported only one death from intracranial hemorrhage among 13 patients not treated surgically. The remainder were alive and enjoying useful and happy lives.

Present Study

In an attempt at further evaluation of the seriousness of bleeding from arteriovenous

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Fellow in Neurosurgery, Mayo Foundation (Dr. Wood). Section of Neurologic Surgery, Mayo Clinic and Mayo Foundation (Dr. Svien). The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

anomalies, we have reviewed the records of 51 patients in whom the presence of such anomalies was demonstrated either by observation at operation or by angiography. Sixteen of the patients, eight male and eight female, experienced 20 episodes of subarachnoid hemorrhage. A number of these 16 patients had attacks of severe headache and subjective nuchal rigidity not requiring medical attention and of less than a day's duration; these short bouts probably represented the leakage of small amounts of blood into the subarachnoid space, but because of their dubious nature they were not included herein as episodes of subarachnoid hemorrhage. The average age at the time of hemorrhage was 31 years. The youngest person in this series was 6 and the oldest 60 years of age. Eight patients bled during the third decade of life. Only three instances occurred in patients less than 20 years of age. The subarachnoid hemorrhage appeared as the initial symptom in 10 of the 16 patients.

Of the 16 patients, 3 had more than one attack of bleeding. The first, female, experienced three such attacks, one in 1932, one in 1936, and the last in 1942. In the first and last attacks she was not unconscious, but in her second attack she was stuporous for five days. When last heard from, nine years after her last hemorrhage, she was alive and well. The second of these patients, male, bled twice, once in 1934 and once in 1936. In the first attack he was unconscious less than a day, and in the second he was unconscious a week. He was alive and productive five years after his last attack. The third patient, male, had two attacks, one in 1946 and one in 1950, and was unconscious both times. He was hemiparetic when last heard from, three years after his last attack.

The histories stated exactly what the patients were doing when the bleeding began in 10 of the 20 episodes: Six were straining or lifting; one had just been struck a blow on the head, and three were quiet, undergoing no physical stress. All episodes were abrupt and sudden in onset. Four were ushered in by a generalized convulsion, and three were associated with numbness of one side of the body or the other just preceding the attack. In all 20 episodes the patient had severe headache at the onset. In about two-thirds of the instances nausea and vomiting appeared early.

The patient was unconscious in 8 of the 20 episodes of hemorrhages, in 2 of the 8 for less than a day. The unconsciousness appeared at the onset of the hemorrhage in each instance. In six of the eight instances the patient recovered, and in two death occurred during the hemorrhage. In 2 of the 20 episodes the patient was stuporous for short periods at the onset of the bleeding, and in 1 other the patient was confused for 24 hours; recovery occurred in all 3 instances. The remaining nine patients remained fully conscious during the attack.

Nuchal rigidity and bleeding into the cerebrospinal fluid occurred in all episodes. In a majority of episodes the patient's temperature increased during the period of active bleeding, although it never exceeded 103 F orally. Monoplegia or hemiplegia, with appropriate changes in reflexes, developed in six of the episodes, in three of which it was permanent. Some degree of aphasia occurred with five episodes. Choked disks were observed in 4 and homonymous defects in the visual fields in 9 of the 16 patients. An intracranial bruit was heard in only 2 of 10 instances in which the skull was auscultated. Arteriographic examination demonstrated the lesion in each instance in which it was performed. Plain roentgenograms of the head showed calcification in the region of the anomaly in 5 instances and no abnormality in 11.

Seven patients had no definitive surgical treatment for their lesion. The two deaths from subarachnoid bleeding occurred in this group, giving a mortality rate of 12.5% for the entire series. The remaining five patients have fared as follows: (1) first symptom in 1932, no bleeding since 1942; (2) first symptom in 1941, no bleeding since;

since; (4) first symptom in 1945, no bleeding since 1950, and (5) first symptom in 1925, no bleeding since 1950. Of these five patients, three have no residual paralytic or speech defects, and two have some degree of residual hemiparesis.

Nine of the sixteen patients were treated surgically. No deaths from bleeding occurred in this group. Four of these patients have had episodes of subarachnoid bleeding since operation.

Comment and Summary

Although this series of 16 patients with hemorrhage is small, certain characteristics of bleeding from arteriovenous anomalies can be deduced. First, the bleeding is not nearly as fulminating as that from cerebral aneurysm; thus, in only 8 of the 20 episodes of bleeding was the patient unconscious, and in 2 of these the period of unconsciousness lasted less than a day. Second, bleeding from arteriovenous anomaly is not nearly as likely to be fatal as is that resulting from ruptured cerebral aneurysm. Third, residual neurologic deficit is neither frequent nor often profound.

Of the 16 patients, 2 died of subarachnoid hemorrhage and 1 died of bronchopneumonia not associated with subarachnoid hemorrhage. Of these remaining 14 patients, 11 are working full time at their usual activities.

It is generally conceded that subarachnoid bleeding from a cerebral aneurysm is an indication for definitive surgical treatment in patients who survive the initial attack and in whom such factors as age are not contraindications. The high mortality rate from repeated bleeding justifies this view. On the other hand, subarachnoid bleeding from an arteriovenous anomaly does not have the same ominous connotation as that resulting from a cerebral aneurysm. Hence, one must be cautious in considering subarachnoid bleeding from an arteriovenous anomaly as an indication for surgical removal of the lesion. Another reason for caution is the appreciable operative mortality rate; this was 11.7% in Olivecrona and Riives' series, a figure which is approximately the same as the mortality rate from bleeding in our series. Furthermore, even though total excision is thought to have been accomplished at operation, long-term follow-up observations may prove this to be untrue, leaving the same set-up for bleeding as before. It should be kept in mind that the residual neurologic deficit in most of the surgically treated patients is bound to be appreciable, because of the frequent location of the anomaly in the vicinity of the Sylvian and Rolandic fissures.

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Case Reports

Multiple Primary Brain Tumors in Opposite Hemispheres of the Same Patient

GEORGE AUSTIN, M.D.; LAWRENCE J. BARROWS, M.D., and FRANCIS C. GRANT, M.D., Philadelphia

We are aware of seven previous case reports in the literature describing multiple primary brain tumors in the same patient.[1-5] Few of these cases have been diagnosed during life, although one has been described in which both a meningioma and an adjacent oligodendroglioma were successfully removed at the time of a single operation.[4] In the case we are about to describe, two primary brain tumors occurred in the same patient but only one of them was diagnosed at the time of operation. The fact that the remaining tumor occurred in the opposite hemisphere made the diagnosis somewhat more difficult, and it was only at autopsy that we obtained evidence of another primary brain tumor. Although this type of double lesion is very infrequent, our purpose in reporting these tumors is not only to add another case of considerable rarity to the literature but also to stress the possibility of such a diagnosis, with the hope that in the future antemortem diagnosis and successful removal may be carried out, with preservation of the patient's life.

Report of a Case

A 47-year-old white man was admitted to the University Hospital complaining of right frontal headaches. The patient was a textile worker who for the past four months had noted generalized weakness and fatigability. Ten days prior to admission to the hospital he had chills associated with nausea and vomiting. At this time his right frontal headache became more noticeable, and he was treated for possible appendicitis by his family physician, who gave him penicillin injections. He then gradually developed a left hemiparesis associated with disturbed mentation and incontinence during the next few days. The headache was relieved for three days following a lumbar puncture but returned with increasing severity. On admission, the general physical examination was essentially normal with the exception of a presystolic murmur over the precordium. The blood pressure was 144/77, with a pulse of 80 a minute. The patient was lethargic and showed left facial weakness of central type, left hemiparesis, a bilateral Babinski sign, nuchal rigidity, and hyperreflexia bilaterally, but more pronounced on the left. There was no papilledema at this time. The visual fields were normal, although the patient cooperated poorly during the examination. It was felt that the patient had a space-taking lesion and a ventriculogram was indicated. The ventricular fluid was found to be clear on both sides, and it was noted that the left ventricle contained approximately 40 cc., whereas on the right side only 8-10 cc. was obtained from a more superficial tap. Three cubic centimeters of sodium indigotindisulfonate U. S. P. (indigo carmine) was injected into the left ventricle and found to come out in the ventricular fluid from the right ventricle. Air was then injected into both ventricles after drainage of all ventricular fluid. The ventriculogram showed a shift of the right ventricle toward the left side, as well as a slight shift of the third ventricle to the left. The left ventricle was larger than the right, and the left temporal horn was noted to be slightly elevated. The films were interpreted as suggesting a right temporal lesion. A right frontotemporal craniotomy was done on June 29, 1953, and a large infiltrating tumor subtotally removed from the right temporal lobe and island of Reil (Fig. 1). Postoperatively, the patient did well for about 10 days and then gradually developed a fever, necessitating removal of the bone flap because of a staphylococcic infection. After this the incision healed, and the patient was discharged on July 29.

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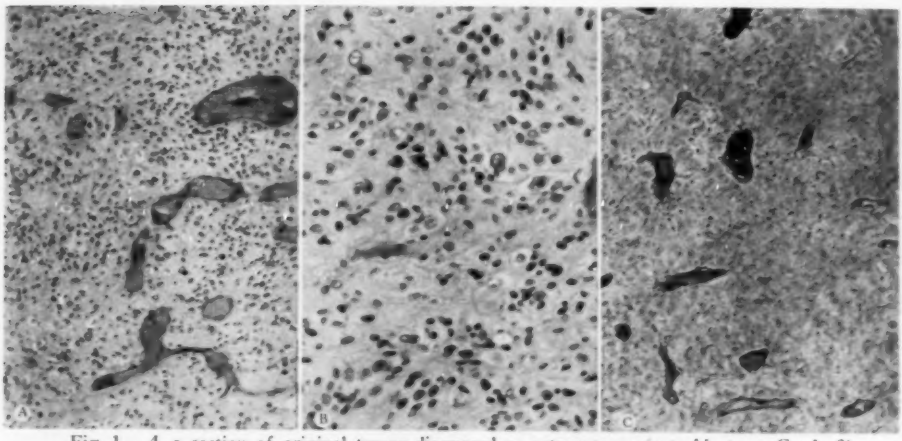


Fig. 1.—*A*, a section of original tumor diagnosed as astrocytoma (astroblastoma Grade 2). Hematoxylin-eosin stain; reduced to 40% of mag. × 200.

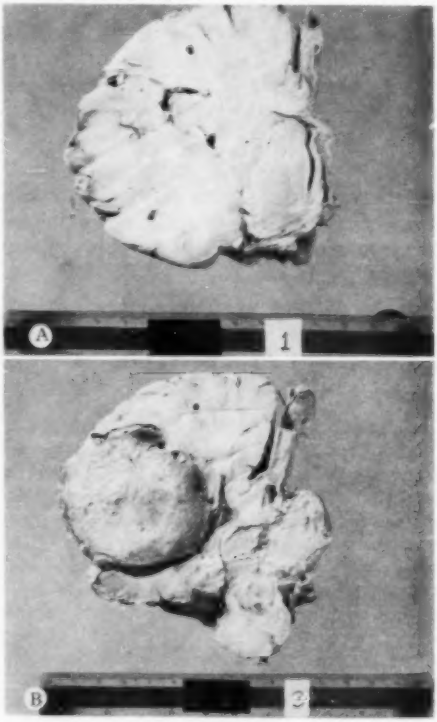
B, round and oval nuclei of varying size and shape but without evidence of necrosis, hemorrhage, or mitotic figures (astroblastoma Grade 2). Hematoxylin-eosin stain; reduced to 40% of mag. × 400.

C, Laidlaw stain for reticulum. Only the reticulin fibrils around blood vessels are stained (astroblastoma Grade 2). Reduced to 40% of mag. × 200.

The patient was readmitted on Oct. 17, 1953, complaining of severe pain in the left arm and leg and complete paralysis of the left arm. He was unable to walk, and there was a moderate amount of atrophy of the left arm. The reflexes were hyperactive on the left side, and there was a Babinski sign on the left. The plantar reflex on the right was one of flexion. There were also astereognosis on the left side and complete agraphesthesia. It was felt that the patient was showing symptoms of further tumor growth, and a right carotid arteriogram was taken. This showed a lack of filling of the middle cerebral group of arteries and multiple abnormal new vessels in the right parietal region, which were thought to be evidence of new tumor growth. On Oct. 24 a total right hemispherectomy was done, with removal of the entire hemisphere except for the thalamus. The patient remained conscious and speaking throughout the procedure and made a fair recovery. However, four weeks following the operation, a discharge from the wound developed and disclosed a subgaleal abscess. This necessitated removal of the tantalum plate, which had been fitted at the time of the hemispherectomy. Thereafter the patient's wound healed satisfactorily, but within a few weeks he began to show signs of mental deterioration with increasing periods of confusion. He developed a progressive aphasia and became completely unresponsive, with extensor rigidity in all extremities. It was thought that this represented spread of the tumor into the left hemisphere. The patient died on April 3, 1954. At autopsy, a large encapsulated tumor was found to be present in the temporal lobe of the left cerebral

Fig. 2.—*A*, gross review of brain of patient at autopsy to show completeness of removal of the right hemisphere.

B, more posterior view, revealing meningioma of the left temporoparietal lobe.



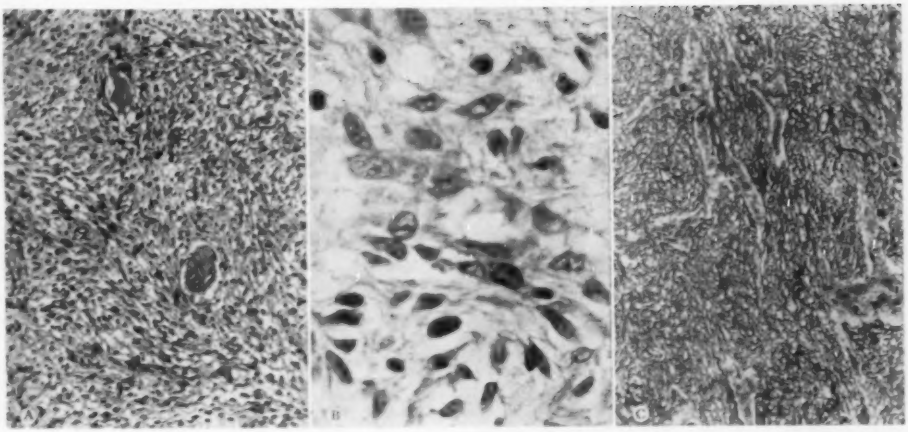


Fig. 3.—*A*, spindle-shaped cells arranged in interlacing bundles and separating islands of meningothelial cells seen in next illustration. Hematoxylin-eosin stain; reduced to 40% of mag. × 200.

B, meningothelial cells with predominantly elliptical or oval nuclei. Hematoxylin-eosin stain; reduced to 40% of mag. × 1160.

C, Laidlaw stain for reticulum. Note the increase in reticulum laid down by the tumor. Compare with that of the astroblastoma. Reduced 40% of mag. × 200.

hemisphere (Fig. 2). The ovoid mass measured 6×5 cm. and was thought to lie predominantly in the temporal lobe, extending superiorly into the parietal lobe. On coronal section, the lesion was seen to be 5 cm. in depth. It was reported as follows by the neuropathologist. "The tumor is very firm and rubbery and suggests a primary meningioma. There is grossly no relation between this tumor and the one previously removed. Microscopically, this is a fibroblastic lesion, most closely resembling a sarcoma, which on special stain is found to be completely filled with reticular tissue. This lesion most closely fits the category of sarcomatous meningioma, Type VI, Variant I" (Fig. 3).

Comment

Although this second tumor was completely encapsulated and probably a removable lesion, it is questionable whether the patient would have had much useful function remaining after its removal. The development of the cerebral symptoms on the left side so late in the course of the tumor is also a strange part of this picture. However, the tumor appeared to have been present for a long time, considering its size and well-encapsulated appearance. It may be that the shift of the intracranial contents to the right side following the hemispherectomy accentuated the symptoms attributable to the second tumor. The fact that the patient appeared to be in a reasonably satisfactory condition for several months following the hemispherectomy, and had even gone so far as to learn to walk with the help of a nurse on one side, suggests that if the second tumor had been extirpated at this time there might have been some chance for recovery. It is also interesting to speculate in this particular case whether the rapidly growing astroblastoma was the tumor truly responsible for the symptoms and neurological deficit which the patient presented. The second tumor, of a benign encapsulated type, appeared to have been present for many years, and may have produced a certain amount of adaptation of the surrounding brain structure, so that the symptomatology was minimal. The original ventriculographic findings of a slightly elevated left temporal lobe probably should have been interpreted more seriously, but the marked shift of the right lateral and third ventricles to the left overshadowed this minimal finding. Finally, we should like to point out again that, although these

tumors occur very infrequently, the possibility of multiple brain tumors in opposite hemispheres should be considered when diagnostic studies or the neurological picture cannot be explained by the primary, and originally detected, tumor.

Hospital of University of Pennsylvania.

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Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Irving C. Sherman, M.D., President
Oscar Sugar, M.D., Secretary

Regular Meeting, Feb. 19, 1957

A Quantitative Method for the Investigation of Aphasia. Drs. Ralph M. Reitan and Robert F. Heimburger, Indianapolis.

The understanding of aphasia can be advanced by two procedures: (1) the routine use of standardized testing techniques and (2) the application of quantitative methods in analyzing the results. Application of such methods can show the relationships between aphasic symptoms and the groupings of symptoms which the relationships support. In the present investigation, each of 458 brain-damaged subjects was tested using the Halstead-Wepman Aphasia Screening test. Results falling in the pathologic range were found in 174 subjects. The symptoms elicited were used to compute a matrix of tetrachoric correlation coefficients. The results showed a striking relationship between many symptoms, but a low or inverse relationship between others. The results will be discussed in terms of the methods used, the composition of the group, and the significance of various symptoms.

Discussion

Prof. Ward C. Halstead: This is the first time that a systematic method of determining language disturbances has been used. There are aspects of this that are little short of exciting. Using this simple method, it is possible that patterns in language difficulties can be isolated which some day will be valuable in eliciting the type of lesion and its location.

Dr. Alex J. Arieff: The authors should be complimented on this task. It seems to me that a long time ago there were some case reports in which they showed patients with aphasia having acalculia who were able to subtract and to multiply but could not divide. I noticed in their tests that they used only subtraction. I wonder if there was any correlation in the various other arithmetical tests.

Dr. Harold C. Voris: My question has to do with the time involved in this procedure. Do you do the entire test in one sitting, and how long does it take if you have no difficulty with the test?

Dr. Percival Bailey: I was interested to know whether some of these things could technically be called aphasia. In apraxia, for example, why do you not have them draw letters? Children have great difficulty in joining parts of A, K, and H together in proper relationship. I wonder if that might do just as well or might exhibit a difference.

Dr. Sherman E. Kaplitz: I believe that two or three of the cases demonstrated were of right-hemisphere lesions. The authors may have had a reason for showing these.

Dr. Robert F. Heimburger, Indianapolis: In answer to Dr. Halstead's question: The patients we have tested have lesions that are quite variable as to type and size. Of course, it would be ideal to test several groups of patients with identical lesions. Since this is impossible with human material, we intend to try to draw meaningful information from a large group of patients with lesions as we find them. This has been done with the various portions of the neurologic examination which we all use.

The right hemisphere was involved in some of the illustrative cases, as one of the discussers remarked. These patients had difficulty with spatial orientation. Although this is not commonly thought of as one of the factors in aphasia, some language functions are made difficult when spatial orientation is altered. By testing for it routinely, we are better able to delineate some of the aphasic symptoms which we encounter. Although many aphasic symptoms arise from lesions in the left hemisphere, certain ones are produced by damage to the right hemisphere. Almost all of the language difficulties arising from lesions in the right hemisphere are related to spatial disorientation.

Dr. Ralph M. Reitan, Indianapolis: With respect to Dr. Arieff's question regarding specific types of losses in arithmetical ability: We are limited in our conclusions to the type of information we obtain with the standard testing procedure. The standard procedure calls only for addition and multiplication. If we find a defective performance, we then vary and extend the examination to be sure that there is a fundamental loss of one type or another of arithmetical com-

putation. Of course, aphasic symptoms are often extremely complex and the losses sometimes highly specific. The procedure which we have followed is not at this point as refined as it might be. Clear defects in arithmetical computations have been grouped under the heading of acalculia, regardless of whether the defect in this area was partial or complete.

With respect to Dr. Voris' question: Approximately 15 minutes is required to administer the test. In some cases the testing procedure may run to 20 or 25 minutes. Because of the short time that is usually required, we rarely see any evidence of fatigue as a factor interfering with performance.

Commenting on Dr. Bailey's observations, we test for writing ability in a number of ways. We have patients write from a verbal stimulus (dictation) and from a visual stimulus that represents the form of an object, and we have them copy printed material. We often find instances in which a patient is able to recognize and express symbolic material involving language, but cannot organize spatial material that does not have language significance. More specifically, we frequently find patients who are unable to copy a simple Maltese cross without distortion of the spatial configuration, although they have no trouble with language functions, including writing. Occasionally we see a patient who is defective in both these respects. In these patients it is our impression that language difficulties, including writing, take precedence over the difficulty with spatial configurations as indicators of damage in the left hemisphere.

The question concerning our presentation of cases with lesions of the right hemisphere prompts me to point out that 29% of our patients had difficulty in copying a cross but no difficulty with language. Rather than run the risk of restricting our findings prematurely, we have examined all patients that are available regardless of location or type of brain damage. Our results suggest that many patients with lesions in the right hemisphere have highly specific difficulties with spatial configurations, just as patients with lesions in the left hemisphere have specific difficulties with aspects of language reception and expression.

Observations upon Regeneration of Axons of the Spinal Cord in Mammals. Dr. Leslie W. Freeman, Indianapolis.

Surgical severance of the spinal cord of the rat and the dog is followed by complete paraplegia. In those animals which can be maintained in excellent health apparent voluntary control of some or all of the movements and sensation of the hindquarters return. Chemical or surgical reserverance of the cord results in return of paraplegia. Electrical stimuli have been recorded through the site of previous section in animals showing functional ability. Histological preparations reveal axons traversing the site of previous section. Implantation of centrally connected nerve roots or nerves through the distal stump of the divided spinal cord can be followed by return of function. Extensive connective tissue scarring at the site of surgical trauma precludes the regrowth of axons.

Discussion

Dr. Harold C. Voris: To break through the barrier of tradition, teaching, and belief in the absence of regeneration of axons in the nervous system is quite an achievement. As far as I am concerned, Dr. Freeman has broken through the barrier, and I believe he has demonstrated that there is such regeneration. I cannot say that I accept all the material shown tonight without reservation, particularly the moving picture. It is obvious that it is likely to be a long time, and perhaps only in isolated instances, before this will be of clinical significance. In the meantime it is extremely interesting. At one point I am interested in what he considered the ideal dosage, in micrograms, of Piromen (a pure carbohydrate derivative from certain bacteria) to the rat or dog. If we were going to treat a human, what would he consider the optimum dose?

Dr. Oscar Sugar: I appreciate from my own experience the enormous amount of work that goes into examining thousands of rats, getting up in the middle of the night, squeezing their abdomens so they will urinate, and getting bitten on the fingers. The application of this work in the human would appear as yet uncertain. Some of our Spanish-speaking brothers have aimed for the same thing in trauma, where the spinal cord has been damaged enough so that the ends cannot come together. They have taken out a vertebra and tried to sew the ends of the spinal cord together in the hope that there might be some regeneration. The trouble with the human body is that the ribs are in the way, and they cannot get the ends together. In later experiments, with pigs, they have taken out not only the vertebra but the rib as well. So do not be surprised if this will come to be a proper procedure in the future in treating human paraplegia.

Dr. Robert F. Heimburger, Indianapolis: I should like to emphasize that the animals which demonstrate spinal cord regeneration have excellent care and minimal complications. It is a mammoth undertaking to keep paraplegic animals alive, during the nine months to a year required for clinical signs of regeneration to develop. Most of the experimental material from which the conclusion that the "spinal cord does not regenerate" was derived comes from animals that died, or were

killed, in six weeks to three months, in an extremely debilitated state. It seems obvious that a body riddled with bed sores and urinary-tract infection will not support any kind of regeneration.

From this we can conclude that a person with a spinal cord injury must have meticulous care, and be kept in optimum condition for well over a year before any clinical indications of regeneration can be expected. Injuries to the human spinal cord are never the clean incision used in experimentation. A long area of hemorrhage and scarring occurs in the usual injury to the human spinal cord, making regeneration difficult. Regeneration does occur, but whether it can lead to useful function remains to be seen.

DR. ALEX J. ARIEFF: It seems to me we ought to see much better recoveries in paraplegics if this were so. It is hard to compare rats with humans. You cannot compare an animal's walking with the human. I can't tell whether the animal is walking or it is a reflex movement. I remember Ransom showed the scratch reflex phenomenon in the dog. Quite enough paraplegics have been operated upon and treated well, at least in the last few years since the Korean war, that we ought to see some degree of recovery. There are so-called physiologic complete lesions; not severances of the cord. The patients were traumatized by contusion or other means, so that the cord was not anatomically severed. In these cases there is sometimes some recovery. We have reported on some of them. About 20% of them would show evidence of sensory and motor recovery, many years later. The longest interval was seven years. But until one gets anatomical and histologic evidence that the recovery is due to regeneration, I do not think one can say regrowth is possible in the spinal cord. However, the roots do recover. They should be able to recover when a root from a higher level is anastomosed to one at a lower level. That is no different from a peripheral nerve. I wonder if this could really be shown by adequate histologic examination in human cases.

QUESTION: Is this related to chordotomy?

DR. LESLIE W. FREEMAN, Indianapolis: I am grateful for the comments and criticisms. We have never been able to translate the Piromen dosage from rats to humans. The rat is resistant to fever, and an equivalent dose would be 250 micrograms. A 15μg. dose would give a human patient a very severe headache. Our method for determining the dosage starts with giving 10μg. intravenously. If there is headache and fever from this, we give 10μg. intramuscularly. Not every rat had the amount of recovery shown here. Results of treatment in spinal cord injuries are not likely to be informative for a long time. We have been using placebo controls, but material collects slowly. We have seen patients who showed results from Piromen, but we think the results may have occurred in spite of the medication.

I have been informed of vertebral anastomosis being done in humans. I agree that one should see some functional recovery in humans. Perhaps you have answered your own question, Dr. Arieff, by your reference to those showing recovery in seven years. It would be impossible for me to say specifically how long return of function could be expected from suspension of physiologic activity. Certainly we see circumstances in which the motor function may be absent for some period, but in the treatment of rapidly growing tumors we are worried about anything that has gone beyond 24 hours in the spinal cord, and we rarely, if ever, see function returning in cases in which it has been gone for this length of time. In slowly growing tumors, function can be abolished for days with return of function after surgery. However, weeks or months of absence of function usually means no return after surgery.

We have been quite reluctant to use stimulation techniques on the human—though we have had opportunity to explore many cords—largely because we find that the hindquarters of animals are difficult to move by stimulation of the cord. We are not very pleased in demonstrating conduction alone because of the many possibilities for artifact. I should be perfectly willing to try it, but I am sure I would not have the answer even then.

A question was asked regarding chordotomy. White and his associates have followed patients with chordotomy over a period of years and have noted patchy return of sensation. They believe it could represent a return of axons in cords damaged by surgery. There have been enough axons which do not look like axons in the normal human spinal cord to make one feel that axonal regrowth probably does occur. Whether regrowth can be brought to a point where it is useful I am not prepared to argue one way or the other at this time. I did skip through the transcripts a little more rapidly than I planned to because I did not want to raise the problems of cerebral orientation. We have monkeys in which we transferred the spinal root innervation from one leg to the other and the monkeys later walked. Those animals were lost by an outbreak of tuberculosis, and we never had opportunity to study the cerebral localization. I believe that cerebral centers are plastic and can be reoriented.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, March 19, 1957

Parenchymatous Cerebellar Degeneration Complicating Diphenylhydantoin (Dilantin) Therapy. Dr. R. A. Utterback, Iowa City.

In an attempt to correlate observed ataxia in patients taking diphenylhydantoin (Dilantin) with histologic changes in the central nervous system, studies were carried out on cats fed diphenylhydantoin. It was found that daily doses as small as 20 mg. (approximately 8 mg/kg.) would produce ataxia in cats. Doses larger than 20 mg/kg. could not long be continued without producing anorexia, bleeding disorders, and death.

The histologic changes were confined to the cerebellum, where doses as large as 30 mg/kg/day produced widespread destruction of the Purkinje cells. Those animals receiving even larger doses were found to have, in addition, diffuse destruction of the granule cells and cystic gliosis in the cortex and medulla of the folia.

Histories were presented for two patients who developed cerebellar ataxia on large doses of diphenylhydantoin and made incomplete recovery after the drug was discontinued.

Histologic changes strikingly similar to those seen in the cats were demonstrated in the cerebellum of an epileptic patient who had received large doses of diphenylhydantoin and died in status epilepticus. The inference is drawn that too large doses of diphenylhydantoin can be responsible for very severe cerebellar ataxia and histologically demonstrable changes in the Purkinje cells and granule-cell layer of the cerebellum.

Discussion

Dr. Roland P. Mackay: We have all seen patients with ataxia following the administration of diphenylhydantoin, resembling those described by Dr. Utterback. There seems little doubt that some patients are more sensitive to the drug than are others, and develop ataxia on much smaller doses. Can Dr. Utterback tell us whether in his experience such a variable sensitivity is found? I should also like to ask whether, in his studies on animals, any changes were noted in other parts of the nervous system than the cerebellum which might serve to explain the lethargy and lack of initiative shown by some of the animals.

Dr. Louis D. Boshes: As Dr. Mackay knows, it is a rare patient who will show this type of response to diphenylhydantoin sodium. This illuminating report by Dr. Utterback can serve as a warning to those of us who treat epileptics regularly. I should like to add an unusual example from a recent experience. I was called to see a man of 65 who had been having sizures since childhood. In the past 40 years he had been taking the same medication, and, of course, this history intrigued me. He, too, presented some definite cerebellar findings; so I thought I had better look into the picture a little more closely. In one way or another I ran down the contents of the prescription, which was as follows: cascara sagrada, grains 40 (2.6 gm.); saccharin, grains 40; phenobarbital sodium (Luminal), grains 270 (17.25 gm.). Ninety capsules were made of this mixture, and the patient was using three capsules daily. In other words, in the past 40 years he had been receiving 9 grains (0.58 gm.) of phenobarbital sodium a day, and this easily accounted for his neurologic picture.

Lastly, I would suggest that, as a practical measure, every patient with a convulsive state should carry a card of identification of himself and his illness. The card should carry adequate information to the effect that the patient is taking certain drugs which might have untoward effects. This would tend to prevent any misinterpretation of a patient's unpredictable objective symptoms.

Dr. Alex J. Arieff: Many years ago Dr. Kaplan and I reported on clinical parenchymatous degeneration. These cases in the Cook County Hospital all had a background of alcoholism. When I presented this report some of the older clinicians were not very pleased to admit that alcohol was the offender.

Dr. Utterback should be complimented on showing that this particular drug is a toxin and may produce irreversible change. I do not know whether alcoholism could produce a similar change, I was struck by the generalized signs. I wonder whether other parts of the nervous system were involved.

Dr. R. A. Utterback, Iowa City: In answer to Dr. Mackay's question: Yes, we did have one cat out of nine that did not become ataxic on the doses that we thought, from experience with the others, should have produced it. Of the nine cats given diphenylhydantoin, only one did not become ataxic on a dose of 30 mg. a day.

There were other evidences of damage in these animals. We did not find other degenerative processes in the central nervous system, but these animals became susceptible to infection; in one we found diffuse encephalitis. In a few of the animals, at least the first two or three we worked with, we had a great deal of difficulty with a bleeding disorder. They would bleed from the gums and from the intestine. We found we could

stop the bleeding by giving multivitamin preparations. This might be an interesting observation to follow up.

In response to Dr. Boshes: I am certain that parenchymatous cerebellar degeneration is a more or less general response to any number of toxins. Our only point here was to make it clear that diphenylhydantoin is one of these toxins and that the toxic effect on the cerebellum was demonstrable histologically in animals and in a patient.

In reply to Dr. Arieff: I would simply say again that we thought the vitamins protected these animals from one of the side-effects. As soon as we started giving vitamin supplements, the bleeding stopped. We did not pursue this further, and I still do not know why it did.

Effect of Tremor-Producing Drugs on Subcortical Electroencephalographic Recordings. Drs. W. W. Kaelber and R. E. Correll, Iowa City.

Electroencephalographic findings of chlorpromazine, reserpine, Tremorine (1,4-dipyrrolidino-2-butyne), and pentobarbital (Nembutal) were studied in 15 cats, using chronically implanted bipolar nicochrome electrodes. Structures investigated were the diencephalon, rhinencephalon, basal ganglia, and allied structures. Possible mechanisms of tremor production were particularly sought.

Chlorpromazine, in contradistinction to reserpine, produced diffuse slow activity, especially from the posterior cortex. This activity was frequently gone prior to occurrence of tremor. Activation of the midbrain reticular system, reported by Himwich and Rinaldi, was never observed with equivalent or higher levels of chlorpromazine.

Occasional seizure-like activity was seen in all three systems following reserpine and chlorpromazine.

Tremorine alone produced a fast record, with voltage increase and spike-like activity, particularly from the posterior cortex. When Tremorine and chlorpromazine were combined, their electrical effects appeared to compete, with the activity alternating between slow and fast. When Tremorine was combined with pentobarbital, fast activity seen with either alone is markedly potentiated from the posterior cortical areas.

Comparison of these drug effects would indicate that cortical activation or activation of the reticular formation cannot serve as a sufficient explanation of the mechanism involved in tremor production. However, under certain conditions, amplitude and persistence of tremor appear to relate to the amount of fast activity present in the posterior cortex.

Discussion

Dr. H. Russell Meyers, Iowa City: I should like to make two observations, referring for their validation to data brought out at the Symposium on the Reticular Formation, held last week in Detroit. The first comment is meant to draw attention to the fact that we tread on somewhat dangerous ground whenever, in our interpretations, we allow ourselves to deal with any part of the nervous system as if it were homogeneous from an electrical point of view. I seem to discern such an effort in the present paper, which deals with a portion of the nervous system loosely designated as "the midbrain." Recent studies have made it clear that the tectum, tegmentum, and crura of the midbrain and their several subsidiary parts do not function as a whole, either electrographically or in a behavioral fashion.

The second point I wish to make is that the evidence gathered up to the present time does not permit us to talk with much confidence regarding the relationship between recorded electrical events in the brain and concomitantly observable overt behavior, normal or abnormal. We have been listening to a discussion of tremor tonight. This form of hyperkinesia is, of course, a peripheral behavioral manifestation, regarding which we have every reason to believe there are corresponding events in the central and peripheral nervous systems. The demonstration and explication of those central and peripheral neural events have been for many years a matter of concern for those of us engaged in research in this area. To arrive at any dependable notions in this connection requires rigorous thinking and the exercise of skepticism. The demonstration of electroencephalographic changes does not in itself permit us to conclude that these changes are equatable with the neural events which subtend tremors. Tremor, as we all know, tends to be a discontinuous phenomenon, appearing and disappearing in trains of various lengths. To relate electroencephalographic changes with tremor, at least two demonstrations are called for: 1. The changes must be present in some close temporal relationship with the tremors, being present or absent when the tremors are evident or not evident. 2. The changes must be shown *to prevail* in relation to the clinical condition of tremors, and *not to prevail* when disorders of the nervous system other than tremors are present. Until and unless these circumstances can be met, we cannot regard the electroencephalographic changes referred to tonight as pathognomonic or as causally related to tremors.

Dr. Paul Bucy: Dr. Kaelber is to be congratulated upon having presented this difficult problem so clearly. There are two essential phases of the problem of tremor. One is the nature and location

of the pathologic processes responsible for tremor, and the other is to know what structures within the nervous system these lesions release to produce tremor. In the past it has seemed reasonably obvious that destructive lesions in the globus pallidus or the substantia nigra or both would release other nervous mechanisms so that tremor appears. It also seemed from the evidence available that the neural structure which carried the nervous impulses that produce the tremor was the pyramidal tract. Because these observations have always been made under difficult circumstances in human beings, and because tremor comparable to that seen in patients has not been produced in experimental animals, we cannot be certain of these conclusions. It is a difficult subject, and one worthy of further intensive investigation.

Discography: Its Comparative Value. Dr. Thomas B. Summers, Iowa City.

Management of the patient presenting with symptoms and signs of nerve root compression in the lower lumbar region may be straightforward and seemingly without incident. There are instances, however, when the characteristic physical findings are equivocal, or at most minimal, and myelography noninformative. Faced with these problems and anxious to decrease long-term hospitalization, we have used discography in selected cases, with gratifying results. In addition, it was felt that some attempt should be made to analyze and correlate the results of discography and myelography with the operative findings. Such a study is in process at the present time.

To date, discography has been used in 20 cases. Seven of the patients had undergone laminectomy prior to examination at the University Hospitals and have been excluded from this analysis. Of the 13 cases submitted to study, operation disclosed abnormalities of the intervertebral discs in 12. Myelography was normal in four cases; of nine cases showing definite myelographic defects accurate localization was obtained in eight. Discography revealed abnormal findings in 12 cases. (In the one patient with normal findings, myelography was normal, and no pathology was demonstrated at operation.) Of the 12 patients with abnormal discograms, accurate localization was obtained in 11, with the triad of criteria—namely, excessive amount of contrast medium injected, reproduction of the clinical symptoms, and abnormal roentgenographic configuration—present in all. In one patient abnormal discs were demonstrated at two levels; however, reproduction of the clinical symptoms was not experienced.

Dr. Oscar Sugar: I was brought up to believe that it was not necessary to carry out diagnostic procedures of this sort when there was pretty good clinical evidence of what the disease might be. I am a bit disturbed that protrusion of the disc between the last lumbar and the sacral vertebrae can produce weakness of the dorsiflexors of the feet, a finding which is contrary to what I have learned. It is because of these anomalies and because I learned the hard way, that I believe that when you look for a protruded lumbosacral disc and do not find one, you had better look for one above as well. I wonder if you have had any other experience with lumbosacral discs which gave atrophy of the extensors of the feet. That used to be a pathognomonic sign of degeneration of the fourth lumbar nerve root.

Dr. Norman B. Dobin: What is the mechanism of production of pain in this procedure?

Dr. Richard Richter: I should like to ask Dr. Summers whether he thinks it might be possible that he is doing harm, or laying the foundation for future trouble, by putting needles into the normal annular ligament?

Dr. Beaumont Johnson: It is a pleasure to see other people try these techniques. I hold a dim view of what can be learned by discography, as Dr. Summers said. Some people stress the advantage of reproducing the patient's pattern of pain. At the time one injects the disc, there is irritation of the nerve root by the protrusion. Actually, you cannot gain much clinical insight from the resultant pain of which the patient complains.

As far as x-rays are concerned, it is difficult to interpret many of these nucleus patterns. I did not find x-rays of much value in our series; yet it is of real value when the dye is seen in the epidural space. This is evidence of a tear in the annulus. Various tricks in obtaining pictures have proved unrewarding in our hands, viz., stereoscopic films in the anteroposterior and lateral projections.

Dr. Thomas B. Summers, Iowa City: With reference to Dr. Johnson's statements: In one patient having two abnormal discs, injection failed to produce pain. At operation the man was found to have a frank herniation at the lumbosacral level. It so happened that three days before I did the discogram his pain had ceased spontaneously. As Dr. Johnson has pointed out, there are pitfalls in the procedure. It is still in its infancy, and it will be interesting to see where it will end in our diagnostic armamentarium.

In reply to Dr. Sugar's question: It is true that most of us, in relying on clinical evaluation, do think of L5 nerve root involvement at the L4-L5 interspace as giving rise to weakness of the toe extensors, and in severe cases the patient may develop a foot drop. We have, however, encountered patients presenting with lumbosacral herniations who had this clinical finding alone. Stahl found 80% correct localization where one diagnostic sign predominated. His figures are

higher than those given by most clinicians. Some speak of a 50% localization clinically. However, 95% of all herniated lumbar discs are at L4-L5 and L5-S1; hence a 50% correct localization is not significant.

As for Dr. Dobin's question, pain can be produced as a result of pressure being built up within the disc, thereby compressing the overlying nerve root. On the other hand, the irritating dye plays an important role in the intensification of the pain. In some patients this pain lasts longer than five minutes. When there was a rent present, the extravasated dye could be demonstrated in the x-ray.

As for the question regarding the puncture of normal disc tissue, this criticism may be raised in the case not only of discography but of any diagnostic spinal puncture. Nearly everyone is familiar with Pease's work on herniation of a disc following lumbar puncture. Perhaps in such instances the discs are damaged as a result of infection.

The development of a herniated intervertebral disc is more than a purely mechanical one. Metabolic disturbances must play a role. Perhaps the actual herniation does come about as a result of trauma.

It would be interesting to employ discography experimentally, injecting the nucleus pulposus with a nonabsorbable contrast medium and obtaining radiographs at periodic intervals in order to note any change in configuration, etc. Swedish workers have done work of this type using the dog's tail, but this is not a weight-bearing organ.

Diagnosis and Treatment of Diastematomyelia.
DR. GEORGE E. PERRET, Iowa City.

The author discussed the diagnosis and treatment of five verified cases of diastematomyelia. Four of the cases presented localized hypertrichosis, characterized by long soft hair in the midline of the back, usually over the region of the underlying spinal anomaly, but not necessarily over the level of the diastematomyelia itself. Associated with it were congenital dermal sinus, lipoma, and skin dimples. One case had a large thoracolumbar myelomeningocele. Neurologic disturbances were present in only three cases and consisted of impaired function of one or both lower extremities, and weakness and paresis of the flexors or extensors of the foot and toes, associated with reflex and sensory changes. Although the obvious cutaneous, as well as bony, anomalies had been present since birth, the neurologic disorders became more evident when the patients started to walk. The diagnosis of congenital spinal anomaly can be made from the clinical examination of the patient, but the diagnosis of diastematomyelia and its exact location depend upon the radiologic and myelographic determinations. The cases presented spina bifida occulta with associated fusiform widening of the spinal canal and other vertebral anomalies. The characteristic bony spicule arising from the anterior portion of the spinal canal and extending into or through the canal is not always present. The cord-dividing septum may be cartilaginous or fibrous in nature. Myelography outlined the midline septum, which divided and fixed the spinal cord, usually in the inferior thoracic or lumbar region.

Treatment consisted of early release of the lesion fixing the spinal cord in the spinal canal by removal of the bony, cartilaginous, or fibrous septum. The patients, all young children, have improved clinically or at least have failed to show progression in their neurologic disorders.

Discussion

DR. PAUL C. BUCY: This has certainly been an interesting and a thorough presentation of this subject of these interesting anomalies. Dr. Perret has stressed the importance of treating these early; otherwise, there is danger of a severe infection developing. One thing which intrigues me, and always has, is this: Most of the anomalies we see in children, and they have been many and various, can be explained on an embryological basis, but this one is a puzzle. Why should a spicule of bone or fibrous tissue completely divide the spinal canal in this position? I do not understand it on any developmental basis.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, April 16, 1957

Delayed and Prolonged Coma After Accidental Exposure to High-Voltage Electric Current.
DR. ERNST HAASE and DR. JOSEPH A. LUHAN.

A 45-year-old maintenance man suffered an electrical shock on June 20, 1955, while working on a high-voltage electrical switch box. The sudden flash of lightning caused him to become temporarily blinded; he complained of blurred vision, dizziness, and headaches and consulted a physician, who made the diagnosis of thermal blepharitis and conjunctivitis. However, the patient was able to stay on his job until July 8. Only his family noted a definite change in his personality. In contrast to his usual energy and self-willed determination, he

appeared quiet, passive, and docile, "as though his will had been broken." In the early morning hours of July 9 the patient got up for a drink of water and suddenly fell to the floor; his right side was paralyzed, and a short while later he was unconscious and remained in deep coma until his death, on June 22, 1956, one year and two days after the accident.

On his admission to the hospital on the night of his "stroke," his temperature was 99 F, pulse 88, respirations 20, and blood pressure 130/80. There were 5,500,000 red and 17,650 white cells per cubic millimeter, with 18% lymphocytes and 4% stab cells. During the first days in the hospital the temperature rose to 104.8 F. Two spinal taps were bloody, but a third puncture, on July 14, yielded a clear fluid under 250 mm. of pressure, with 3 cells per cubic millimeter, a straight colloidal gold line, and 60 mg.% of total protein.

On July 15, when one of us (E. H.) saw him in consultation, he looked like a person resting in sound sleep, with a relaxed facial expression, rosy color, and easy breathing. There was no stiffness of the neck. The pupils were round and equal and did not react to light; corneal reflexes were present, though not brisk. No papilledema. Face symmetrical. When the lips were touched, the patient responded by pouting them as in an abortive sucking reflex, an ominous sign. The arms and legs appeared paralyzed, with the hands held in slightly bent position, and the right leg turned outward and the foot supinated. Abdominal reflexes were absent, cremasteric weakly present, patellar and Achilles present. A Babinski sign could be elicited on the right side. There was no response to painful stimuli except to pricking of the nasal mucosa. My diagnosis was that of an encephalopathy involving mainly the midbrain and the brain stem, quite likely resulting from an electrical shock injury to the brain.

Dr. Joshua Speigel, who saw him on Aug. 13, confirmed the clinical findings, but on reexamination on Aug. 25, he found decerebrate phenomena, such as rigidity and the Magnus and de Kleijn phenomena. His final impression was that of pontine lesion, either thrombotic or hemorrhagic, on the basis of electrical injury to the basilar artery.

During the following month the patient fell into deep stupor. Two electroencephalographic studies, in December, 1955, and February, 1956, showed a 61 to 8-per-second frequency with some low voltage. There was irregular, slow activity in all areas. No reliable focus was found. The patient was blinking.

A urinary infection with high fever in September, 1955, necessitated administration of antibiotics; a severe diarrhea was controlled by chloramphenicol (Chloromycetin). In May, 1956, the patient developed signs of aspiration pneumonia, with a temperature of 105 F. and a pulse of 150. He died on June 22, of cardiac failure.

The general necropsy findings, apart from those in the brain, were myofibrosis and eccentric hypertrophy of the heart, evidence of congestive failure, and arteriolonephrosclerosis; the aorta was not remarkable, although there was some intimal thickening of the coronary arteries. There was marked cerebral arteriosclerosis, confined largely to the vertebral and basilar arteries, with ancient thrombosis of the middle third of the basilar artery. Sectioning of the brain revealed massive anemic encephalomalacia of the midbrain and rostral two-thirds of the pons, together with some softening in either thalamus, more extensive on the left side. The cerebral cortex appeared macroscopically intact, but microscopic preparations disclosed old partial softening in the right visual cortex. The medulla oblongata revealed complete descending degeneration of the pyramids and marked gliosis (pseudohypertrophy) of the olives.

This case is interesting because of the question of a connection between electrical trauma and belated death. The history and clinical course are highly suggestive of such a connection. The sudden collapse of the previously healthy patient had obviously been caused by an occlusion of the basilar artery. It is impossible to determine how much the electrical injury had contributed to the damage of the arteriosclerotic vessels and had been a factor in precipitating the thrombus formation, perhaps by causing hemorrhages into the diseased intima. Some cases discussed in the literature lend support to the assumption of pathologic changes in the cerebral vessels by electrical trauma.

Discussion

DR. FREDERIC GIBBS: The electroencephalographic changes in this case are not enough to indicate stupor of cortical origin. They are consistent with stupor of diencephalic or hindbrain origin. There are all sorts of detailed differences among various functional states which we call stupor and coma.

DR. IRVING C. SHERMAN: This patient happened to be on my service at the Cook County Hospital. I recently got a subpoena to a hearing at the Industrial Commission. I had hoped Dr. Haase would come out with a more forthright statement that I could use. There is ample evidence in the literature to support the assumption that there is such a thing as prolonged coma due to electrical current, and here is pathologic material to prove its existence.

While this man was on the ward at Cook County Hospital, for a long time there was an argument whether he had a high brain stem lesion or whether the case represented diffuse degenera-

tion of cortical tissue. This problem is not an uncommon one. If I remember correctly, some persons on the ward thought this case represented diffuse cortical damage rather than a lesion in the brain stem. In the last month I have seen two cases in which diffuse coma appeared and in which the argument was raised whether we were dealing with diffuse cortical damage or a lesion in the brain stem. For me it is often difficult to differentiate these two lesions. In this case I felt we were dealing with a high brain stem lesion, for the reasons already presented.

DR. JOSEPH A. LUHAN: I do not know how one would solve this problem clinically. I think the electroencephalogram might help, because with widespread cortical damage one is more likely to get an extremely abnormal electroncephalogram. In this case the findings in the electroencephalogram were not remarkable. I marvel that a man could be so long and severely comatose and still present so little evidence of brain damage in the electroencephalogram.

DR. FREDERIC GIBBS: This man's brain waves were not abnormal enough to account for his clinical symptoms. Dr. Luhan has stated the situation perfectly.

DR. ERNST HAASE: It is interesting to note that all clinical consultants on the case—Dr. Speigel, Dr. Sherman, and I—independently, had hardly any doubt that there was a causal connection between the accident and the death. When arteriosclerosis of the basilar arteries was found post mortem, we had to review the whole case in our minds. This 45-year-old man, with a perfect working record, had not shown any clinical evidence of arteriosclerosis of the brain before the accident. In fact, he continued working for more than two weeks after the accident, and only his family then noticed a change in his personality. Since the man was unconscious for over a year, until he died, it is difficult to determine exactly what had happened to his vessels during this year of coma and various infections. Even admitting that some of the arteriosclerotic changes of the basilar arteries date back before his accident, the impact of the injury and its importance in producing a thrombotic occlusion cannot be overlooked. For the patient, it may mean the difference between life and death.

Central Pain Associated with Cerebral Arteriovenous Aneurysm. DR. MILTON TINSLEY and DR. I. JOSHUA SPEIGEL.

A case of intractable pain, burning in nature, involving the posterior portion of the tongue and throat, was presented because of the unusual features precipitating this painful state. The patient sustained a cerebral hemorrhage, which later was found to be the result of a congenital arteriovenous malformation in the right postparietal cerebral cortex. The pain began after the cerebral hemorrhage. The patient had been entirely free of pain prior to the acute episode, which resulted in a residual left hemiparesis, hemiastereognosis, and loss of proprioceptive sense in the left upper and lower extremities. The arteriovenous malformation was surgically excised without any change in the neurologic status of the patient or improvement of the pain.

This painful state was correlated with a similar case presented by Dr. Silver in the *Journal of Neurosurgery*. The patient presented by Dr. Silver had pain in the contralateral upper extremity associated with an arteriovenous malformation. He was able to demonstrate accentuation of the pain by manipulation of the vessels running into the malformation, and the pain subsided completely after the malformation was resected. In this case, the pain persisted in spite of resection of the lesion. The hemorrhage had resulted in marked cerebral destruction. In spite of various forms of therapy, including injections into the region of the throat, section of the glossopharyngeal nerve, and even psychiatric therapy, the patient continues to have the intractable pain, which has become incapacitating. The mechanism of this pain and the treatment for this pain were open for discussion.

Discussion

DR. HAROLD C. VORIS: Since I have a personal interest in this case, and also quite a folder of letters from this patient, I should like to discuss the paper.

Dr. Tinsley is correct when he says that section of one glossopharyngeal nerve did not cure the patient's pain. It is not true that it was entirely unrelieved. She had no pain in the throat, but the pain migrated to the tongue in a short time. She has used ice chips and many other things to relieve the pain. It is of some interest that the pain migrated to the tongue after the operative procedure which we had hoped would relieve her pain. The most striking thing about the patient is her psychologic reactions. In addition to writing numerous letters, she has attempted to sell her story.

The psychologic mechanism has been studied extensively by Dr. McLaughlin. Whether this patient's pain is due to a central lesion or whether she has pain that cannot be relieved by the standard procedures, I do not know. It has been a very distressing case to everyone connected with it because of the woman's anxiety for relief. She seems to have some insight arising out of her nursing training, but she is a person of rather shallow affect. Her husband died two months

ago, of coronary thrombosis, an event which has added to her emotional situation.

Dr. Percival Bailey: Why not inject procaine into the frontal lobes and see what effect that will have on the pain?

Dr. Milton Tinsley: In thinking of the emotional part of this case, I do not believe one could ever separate emotion from disease. When you have a distraught patient, there is always an emotional overlay, which still does not change the fact that she has pain. Whether it emphasizes the pain or not is of no great importance.

In answer to Dr. Bailey: The patient has suggested that she be subjected to lobotomy. I have been very loath to do that. I do not know what effect procaine has on the brain. I wonder whether one can really get a lobotomy by injecting procaine. Every time I try to put procaine into the brain, it comes right back into the needle. I have never been able to make it stay.

Problems in Cerebrovascular Disease. Dr. E. S. Gurdjian, Detroit.

The material to be discussed includes cinemicrophotography of the pial circulation of the rhesus monkey and certain compression tests of the carotid bifurcation.

Cinemicrophotography of the pial vessels in the monkey reveals that these vessels, 40μ to 150μ in size, are responsive to changes in carbon dioxide and oxygen and changes in cardiac output, but they do not appear to be responsive to stimulation of the sympathetic chain, the seventh cranial nerve, and the central portion of the vagus. A 40% increase in the size of the pial arteries was noted on CO_2 inhalations. A 15% to 20% decrease in the size of the vessels occurred on inhalation of oxygen. There was no question that pial vessels of this size were contractile and distensible, but an actual neuromechanism controlling their size and tone, as in the peripheral circulation, could not be established by this technique.

Compression of the carotid bifurcation may result in syncope in some patients. This may be due to (1) a sensitive carotid sinus; (2) cerebrovascular insufficiency due to thrombosis or narrowing of the contralateral internal carotid or poor communications at the base, and (3) a combination of irritable carotid sinus and cerebrovascular insufficiency. We find that a majority of patients who have syncope due to compression of the carotid bifurcation have cerebrovascular insufficiency rather than an irritable carotid sinus.

Discussion

Dr. Percival Bailey: I remember that when the Germans first began to make sections of the vessels of the brain, they noticed two definite states. In one the branches came off at an acute angle, like the limbs of an elm tree. In the other the branches came off at a right angle, like the limbs of the oak tree. In looking at the slides shown by Dr. Gurdjian, it appears that the branches come off at a right angle. I wonder if that is correct.

Dr. E. S. Gurdjian, Detroit: That is correct. The arteries appear redder than the veins, and pulsations in the arteries are more definitely seen than in the veins. Probably one reason for the tributaries joining larger veins at an acute angle is that in the case of veins we are dealing with less pressure, whereas in the arteries there is a dynamic mechanism behind the flow of blood, causing the branches to arise more nearly at right angles.

Dr. Meyer Brown, Evanston, Ill.: Have you noticed any injurious effects from compression of the carotid artery?

Dr. E. S. Gurdjian, Detroit: In one instance the electrocardiogram became more abnormal after compression of the carotid. If one were to observe the pulse rate at the same time as the compression, one would conclude, in my opinion, that the method is not dangerous. Some investigators have done unusual things. They have put a cuff around the patient's neck and kept the pressure up until after the patient became unconscious. It is interesting to note that both the electroencephalogram and the electrocardiogram may show improvement and some patients recover from the syncope while the carotids are shut off. I think we learn a great deal with compression tests. It is well to know that syncope can occur on carotid compression in persons with a mass lesion. In our series there was unexpected response in 16%. In the remaining patients, carotid compression correctly showed the presence of cerebrovascular insufficiency.

Dr. Roland P. Mackay: Dr. Gurdjian's report is very illuminating and instructive. I believe he would agree that we need to emphasize the difficulties of interpreting the physiologic changes following "carotid sinus pressure." As he has pointed out, occlusion of the carotid artery and irritation of the carotid sinus may cause similar symptoms, which, nevertheless, must be differentiated.

Dr. E. S. Gurdjian, Detroit: I think that is very true. In the last edition of Best and Taylor's "Physiological Bans of Medical Practice," it is stated that compression of the neck, producing syncope, is due to carotid sinus hypersensitivity, and this is not true. It is interesting to note that compression studies have been carried out for over 150 years. One of the earliest records is that of Parry, a little before 1800, which discusses carotid compression and its value in treatment of various ailments. Professor Vanzetti, in 1845, discussed the use of carotid compression for arteriovenous aneurysm in the cavernous sinus. He said that his patient was blind in the affected eye and recovered

vision at the end of a week of intermittent carotid compression. It seems that this (return of vision) may be an exaggeration.

Up to 1900 the belief was that carotid compression resulting in syncope produced cerebrovascular insufficiency. From 1920 on, with the work of Hering and Heymans, the concept of carotid sinus sensitivity became popular. Now we have come to believe that more than four-fifths of these effects are due to cerebrovascular insufficiency.

DR. JOSEPH A. LUHAN: Have you done any work with vasodilators, like nicotinic acid?

DR. E. S. GURDJIAN, Detroit: We have no results, but we are working on them. There is a tremendous amount of work to be done. As I mentioned to Dr. Gibbs this afternoon, it has taken us six years to get what I have shown. This is a good method of study, and if more people were interested in it, we would be able to find out a great deal more about cerebral circulation. Probably this method is not as accurate as some others, like electroencephalography or other electronic methods; nevertheless, what you saw in this movie rather refutes the material in texts on physiology of cerebral circulation. If our conclusions are correct, the material in the textbooks should be changed back to the concepts of Sherrington, Bayliss, Florey, and others, who concluded that the cerebral blood vessels were not affected by neural mechanisms.

DR. J. PATRICK EVANS: These were beautiful demonstrations. I have just had occasion to review some work done with Donald MacEachern in the 1930's on cerebral arterial occlusion, in which we applied silver clips to the middle cerebral artery near its point of origin. We found a great deal of damage to cells distal to the clip and rather generally distributed in the course of the middle cerebral artery supply. Do you think there is a profound difference in tissue damage peripherally and that which develops nearer the origin of the vessel? When we injected the carotid artery central to the point of bifurcation of the middle cerebral artery, we found the injection material appearing on the distal side of the clip. This does not, of course, mean that severe oxygen want had not occurred distal to the clip while collateral circulation of equivocal efficiency was being established.

In view of the findings which you have demonstrated with the Sudan black injections and the other evidence that vessels respond adversely to noxious agents, among which some of the radiopaque materials must be included, I wonder what material you are currently using for angiography.

DR. E. S. GURDJIAN, Detroit: We use diatrizoate (Hypaque). With a clamp on the middle cerebral artery, there should be some contraction of the vessel because there is less intravascular pressure than before. In our movies, after occlusion of both carotid arteries in the neck, the vessels became 10% or 15% smaller. Later, as collateral circulation became reestablished, they were larger, but pulsations never returned during about one hour's observation. The problem of angiography is important. I know that many of you believe angiography to be dangerous, particularly in patients with cerebrovascular disease. We think we can use diatrizoate with no or little difficulty. We found in animals that there is involvement of the intimal lining of some of the vessels when iodopyracet (Diodrast) is used. There is destruction of the blood-brain barrier, which permits the dye to go through, while with diatrizoate the blood-brain barrier remained intact. If we could find a more innocuous preparation for angiography, we would do still better. Angiography is valuable in the management of these cases. The question arises whether or not there are communications between the arteries and the veins on the cortex. This could be definitely established with a better technique than we have now. If one could expose 500 or more frames per second, the injected material might be followed from the arteries into veins if there are such communications.

DR. HAROLD C. VORIS: Do you think that the occasional temporary failure of filling of the internal carotid artery, or one of the branches, is due to spasm of the vessels or to the temporary accumulation of particulate matter, as you showed in the film?

DR. E. S. GURDJIAN, Detroit: I think this possibly could be established. If the vessels are well shown and if, after 12-15 cc. of the medium is injected a certain branch is not seen, it is likely that there is an obstruction or an absence of the vessels.

DR. HAROLD C. VORIS: I am asking about the anterior cerebral artery that does not fill when one injects but fills a few minutes later in the serial angiogram. That is, in a later film with the same injection, the artery fills along with the middle cerebral artery. Is that due to temporary spasm or to temporary obstruction?

DR. E. S. GURDJIAN, Detroit: Some of my friends have attested to the fact that they have seen spasms of the vessels at the base of the brain. I think there is greater likelihood that this is an artifact rather than on a neurogenic basis.

QUESTION: Have you tried Hypoform?

DR. E. S. GURDJIAN: No, we have not. Dr. Geiger mentioned that in his preparations he used an electric current across the head, with an increase in blood flow.

DR. FREDERIC GIBBS: The convulsions were tremendously increased, and the cerebral blood flow was increased. Geiger said that with the convulsions there was a great increase in cerebral blood flow.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND SECTION OF MEDICINE, AND NEW YORK NEUROLOGICAL SOCIETY

John McDowell McKinney, M.D., Chairman, Section of Neurology and Psychiatry, Presiding

Joint Meeting, Feb. 19, 1957

Cerebral Vascular Diseases: Ten-Year Experience with Use of Anticoagulants in Certain Cerebral Vascular Syndromes. Dr. Ellen McDevitt, Barbara W. Gatje, Dr. Stefan Carter, Dr. William T. Foley, and Dr. Irving S. Wright.

Data have been developed which demonstrate that anticoagulant therapy, when properly used in carefully selected cases, will markedly reduce thromboembolic complications and recurrences of cerebroembolism. Types of cases under study include those of rheumatic heart disease with atrial fibrillation, atrial fibrillation from other causes, arteriosclerotic and/or hypertensive heart disease, and other diseases causing cerebral thrombosis or embolism. Details were presented. In summary, during a total of 2503 patient months without anticoagulant therapy, 83 patients experienced a total of 295 thromboembolic episodes, 114 of which were cerebral in location. On anticoagulant therapy, during 2202 patient months, with these same patients acting as their own controls, 31 had a total of 68 thromboembolic episodes, 15 of which were cerebral. Thirty-five of these episodes, including nine cerebral, occurred when prothrombin times were below 25 seconds.

Indications for anticoagulant therapy include the following:

1. Embolic conditions, e. g., fibrillating heart—myocardial infarction with mural thrombus
2. Intermittent insufficiency of vertebral-basilar system
3. Intermittent insufficiency of carotid system
4. Thrombosis in vertebral-basilar system
5. Thrombosis in carotid system—prevention of propagation
6. Thrombosis in cerebral artery branches—prevention of further strokes
7. Multiple or slow strokes

Contraindications for anticoagulant therapy include the following:

1. Usual contraindications for anticoagulant therapy
2. Evidence of bleeding, in spinal fluid
3. Evidence of intracranial pressure
4. Maximum neurologic deficit
5. Extreme hypertension

Discussion

Dr. H. Houston Merritt: We neurologists are pleased that the internists are now joining in the study of these cases, for it is only through cooperative work that we can hope to arrive at the solution of the problem. It should be emphasized that the administration of anticoagulants is prophylactic and that they are not given with the hope of improving the existing defect. They are given to prevent subsequent lesions. The use of anticoagulants in the treatment of patients with cerebral vascular lesion is new, and there is very little literature on the subject. The data compiled by Dr. Wright are the most extensive, and those of Milliken are probably next. As Dr. Wright has stated, there are several categories where it seems that the use of anticoagulants is most promising. The first, of course, are those cases in which there is evidence of intermittent insufficiency of the circulation in the territory of the carotid or basilar artery. The use of anticoagulants does seem to tend to prevent the recurrence of symptoms. Anticoagulant therapy is effective in two other well-recognized types of cerebral vascular lesions, namely, emboli, and thrombotic insults that seem to occur in rapid succession.

If anticoagulants are effective, probably every person with thrombotic or embolic phenomena should be treated by such an agent, but there are patients who have a stroke and do not have a second attack for 5, 10, or 15 years. It would be heroic treatment to give these patients anticoagulants over so long a period. Most physicians have come to the decision that anticoagulant therapy is not indicated in a patient with signs of an occlusive phenomenon in cerebral vessels who is otherwise healthy and who has no evidence of a focus for an embolus.

Anticoagulant therapy, once started, would probably have to continue for the life of the subject. That is probably true for the patients with embolic lesions, but I believe that there are some patients with cerebral arteriosclerosis who seem to go through crises in which their circulation is in some way disturbed, so that they are apt to have thrombotic phenomena. If we can tide them over this period, then the administration of anticoagulants may be stopped.

I know there are a great many physicians in the audience who would like to hear more about the differentiation of a cerebral hemorrhage from a cerebral thrombosis.

I should like to close by emphasizing that anticoagulant therapy is only a stopgap. This is said not to deemphasize the importance of the method

but to call attention to the fact that the solution to the problem of cerebral vascular lesions is dependent on the discovery of the cause of arteriosclerosis in general, which is the main cause of cerebral vascular disease.

DR. JOHN MCDOWELL MCKINNEY: Most clinicians worry that they are going to promote hemorrhage by giving anticoagulants. I wonder if there is any neuropathologist in the audience who has seen any instance in which an anticoagulant has contributed to the death of the patient.

DR. JACK LONDON, Brooklyn: In Dr. Stevenson's neuropathology laboratory at Bellevue we have seen brains in which there had been intracerebral hemorrhage in concentric layers of old and newer hemorrhages. Review of the case histories revealed that anticoagulants had been administered. The newer hemorrhages superimposed on the older hemorrhage were undoubtedly due to anticoagulants. It is for this reason that anticoagulants should not be used. Dr. Wright has stated that if the cerebrospinal fluid is negative for blood, anticoagulants can be administered. Evidences of intracranial hemorrhage may not appear in the spinal fluid unless the rupture of the vessel occurs close to the cortex or the blood has ruptured through the arachnoid tissue. Dr. Merritt stated that 85% of cerebrovascular accidents show blood in the cerebrospinal fluid. In 15% of the cases no blood cells may be found in the cerebrospinal fluid, and yet there is hemorrhage in the intracerebral tissues. I feel that no anticoagulant should be used unless there is definite certainty that no hemorrhage is present. Cerebral angiography should always be performed to help rule out that 15% possibility of intracerebral hemorrhage with no blood in the cerebrospinal fluid.

DR. IRVING S. WRIGHT: As we pointed out in our presentation, any evidence of bleeding is a definite contraindication.

DR. ABNER WOLF: I have nothing to add. I am at a disadvantage in not being able to distinguish between the hemorrhage that comes first and one that is superimposed upon it very shortly thereafter. I do feel, and from what he has said, I am certain that Dr. Wright is of the same opinion, that anticoagulants should not be given in the presence of hemorrhage into the brain.

DR. IRVING S. WRIGHT: We agree that the way to solve most of these problems is to learn how to prevent atherosclerosis.

The question of the determination of which patient is having a hemorrhage without embolism or thrombosis, which patient is having a thrombus without hemorrhage or embolism, and which patient is having both is, of course, the key question. We have to do the best we can, as we do with any other problem in medicine. Once a patient has passed the acute episode, and provided he did not have bloody spinal fluid, there is a good chance that he did have a thrombus or an embolus. Our problem then is to try to prevent future episodes. If he has had more than one episode, our experience is that he is fairly apt to have a series of them at irregular intervals. Our policy, therefore, is that if a patient has more than one episode, he should be on long-term anticoagulant therapy. If he has had only one, you can wait for a second and pray that it is not going to be fatal. This may follow soon after, or there may be an interval of several years. Your decision will be partially a philosophic and partially a scientific one.

Surgical Treatment of Spontaneous Intracerebral Hemorrhage. DR. LEO M. DAVIDOFF.

In young people who are otherwise well but present themselves with an apoplectic picture, particularly if there is bloody spinal fluid, the chances are that the hemorrhage is from a vascular anomaly, and the removal of the clot may also make the removal of the anomalous vessel possible at the same time, with good results and with no or very low mortality. In the case of patients whose hemorrhages are associated with hypertension and arteriosclerotic vascular disease, the results are obviously less happy. On the other hand, failure to treat these people by anything short of operation is so close to 100% fatal that operation, even if very risky, is still worth undertaking. I should like to make a plea, however, for early diagnosis and prompt institution of surgical intervention, in order to obtain the best results.

Discussion

DR. JOHN MCDOWELL MCKINNEY: I am sure that all of us who have to deal with these things are only too anxious to have any light shed upon the time when we must call in the surgeon and when we must get along without the surgeon. I think Dr. Davidoff has helped us here. Is there any discussion?

DR. H. HOUSTON MERRITT: Dr. Davidoff has emphasized the high rate of mortality of cerebral hemorrhage. The vast majority of patients with cerebral hemorrhage will die within a few hours or days, and anything we can do to lessen this mortality is of great importance. The first group of cases does not need discussion because it is evident that operation is the method of choice and is life-saving. The second group, the patients with cerebral arteriosclerosis, hypertension, and intracerebral hemorrhage, is an important one, and examples of this group are seen every day in the medical wards of general hospitals.

Dr. Davidoff did not discuss the criteria for operation or the time for operation. I should like to state my opinion on these questions and see if he agrees with it. The vast majority of patients with a large intracerebral hemorrhage are going

to die within a very short while, regardless of whether an operation is performed or not. An operation may be considered by some people as an undue burden to a patient in this very crucial period. It is our feeling that if the patient withstands the initial shock and lives for two or three days and continues to show signs of increased intracranial pressure, such as choking of the discs and headache, then the chances of saving the life of the patient by an operation are greatly increased. Also, the chances of lessening the severity of neurologic residuals are better. There is also an ethical problem as to whether to operate upon these patients or not; that is, what kind of a person are you going to have left if you keep him alive? Dr. Davidoff has shown that a substantial number of those that he did keep alive were able to lead a productive life for a number of years.

Dr. Davidoff presented some facts in his paper that Dr. Wright did not have time to go into, that is, some of the diagnostic methods that are of value in the differential diagnosis of cerebral hemorrhage and cerebral thrombosis. The electroencephalogram, if followed from day to day, will give valuable information. The information obtained by arteriography will in most instances be definitive, but most of us hesitate to take arteriograms routinely on patients with known cerebral lesions for fear the dye will irritate the vessels and increase the extent of the damage. This paper is of importance in that it shows how surgery can save the lives of some patients with intracerebral hematomas and decrease the severity of the neurologic deficit in the patients who survive.

Dr. Leo M. Davidoff: I thank Dr. Merritt for his discussion. He brought out an extremely important point which I did not want to take time to cover in the paper; that is the question of when to operate. I think we neurosurgeons are inclined to be influenced in cases of this kind by our most recent experience with similar cases; and when we have just had a patient who has been in pretty serious condition and has had an operation for the removal of a hematoma and has made a good recovery, we are stimulated to operate upon a subsequent patient more readily than if the last one we operated upon had died. The cases in which we can wait for several days are, of course, the more favorable ones. However, particularly in a large city hospital, we see patients who come in already in extremis. They are deeply comatose; they are in Cheyne-Stokes respiration; they are cyanotic; they show very marked resistance of the neck, and the cerebrospinal fluid is extremely bloody, with a high red blood cell count. The problem of whether to operate or not is one that is settled by the powers above, for if we do not operate they are definitely going to die; and in the face of that, and with the remote hope that one out of many might be saved, we are often tempted to operate. When we are exploring the possibilities of surgery in a relatively new field, we are likely to be less selective in the type of patient we operate on. After we gain a considerable amount of experience, we are likely to exclude the patients who are most certainly going to die and try to confine our procedures to those who have a better chance for survival.

Stellate Ganglion Block in Cerebrovascular Disease. Dr. Emery A. Rovenstine.

Blocking the stellate ganglion in the management of cerebral vascular accidents is not popular in this section of the country. During the 20 years since Leriche introduced the idea, the experimental laboratory has failed to establish that interruption of the sympathetic fibers at the stellate ganglion produces cerebral vasodilatation or increased cerebral blood flow.

Clinical reports have favored the use of the technique. In the experience here, in some 20% of a small series (36) favorable effects have been noted. These blocks were completed for patients whose diagnosis was embolism or thrombosis and were made in the first 24 hours of the emergency. Results with chronic cases have not been encouraging.

Discussion

Dr. Thomas J. Bridges Jr.: Dr. Rovenstine has indicated the declining enthusiasm for stellate block therapy of cerebrovascular disease. Drs. Yahr, Clark, and I, using a plethymographic technique, have found that superior cervical ganglion block produces slight cerebral vasodilatation, whereas stellate ganglion block produces shunting of a small amount of blood from the brain to the arm.

Dr. Emery A. Rovenstine: In other studies that were concerned with what happens with the solutions when stellate ganglion block is done by the technique we use at the present time, we have found that the solutions injected do not bathe the stellate ganglion only, but travel up and reach the superior cervical ganglion, as well as travel down. In the technique of this block we favor trying chain as we can, by taking advantage of gravity, to get as wide a spread along the sympathetic speed of injection, and so on.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

Joint Meeting, March 12, 1957

Some Statistical Drifts and Backgrounds of a Psychiatric Program. Dr. Henry Brill and Mr. Robert Patton.

Mental hygiene institutions form only a part of the total pattern of psychiatric services, but certain trends in their statistics may be of importance for general planning. The following stand out in New York State figures:

Increase in Geriatrics.—Patients over 65 years of age were 13.3% of first admissions in 1912 and 40% in 1955.

Increase in Child Psychiatry.—In the state hospitals, patients under 15 still have the lowest age-specific admission rate, but it is 10 times as high as in 1920; in the state schools, the percentage of admissions of children under 10 years doubled between 1940 and 1955.

Mortality and Span of Hospital Life.—The mortality is decreased and the duration of hospitalization increased in all categories.

Accumulation of Handicapped and Physically Disabled.—The above trends swell the number of handicapped, while well-retained cases responding to new methods are released faster than ever before.

Rise in Costs.—This has been due to cost of newer therapies, rising standards of care, the growing proportions of handicapped patients, and rising wages.

Halt in Population Growth.—For the third straight year the state hospital census shows a fall of 500 or more, in place of the average previous annual rise of 2000. State schools continue to grow.

Emerging Patterns in Child Psychiatry. Dr. Lauretta Bender.

Child psychiatry began with the care of mentally defective and epileptic children in public institutions and their evaluation by psychometric tests and electroencephalography. It was soon realized that such children also had other problems, including organic brain disease, a poor social and school adjustment, and behavior disorders, which are also associated with all other maladjustments in childhood. Mental, educational, and emotional retardation are the common factors in all psychiatric problems of childhood.

Child guidance clinics were started to treat the behavior problem or neurotic child, with the hope of preventing the institutional care of the delinquent, criminal, and psychotic, through the relationship between the child and the parent, which can be treated by psychotherapy, oriented chiefly by the concepts of Adolf Meyer, Freud, and Harry Stack Sullivan.

Public hospital wards were first opened to care for the children with behavior problems arising from the epidemic of encephalitis following World War I. Diagnostic methods based on maturational concepts in neurology, mental development, perceptual motor patterning, and social-emotional areas or personality made possible a differentiation between those children who had suffered from early deprivation, with resulting psychopathic development, and the brain-damaged children, the schizophrenic, and the children with maturational lags in language. This also led to specific goals for management, training, and treatment programs.

However, public facilities are needed in each community to afford care for maladjusted children and adolescents, irrespective of diagnosis, behavior pattern, or intelligence level. Such a total outpatient-inpatient facility should be in close relationship with homes, schools, churches, courts and all social agencies, medical facilities, and university research and training facilities of its own community.

Patterns in Planning a Psychiatric Program for the Aged. Dr. Alvin I. Goldfarb.

The increased number of aged persons has prompted the development of new services to meet their needs. Many aged persons need comprehensive medical care in which psychiatry plays a leading or an ancillary role. This can be given either in or outside a hospital; socioeconomic factors most frequently dictate how and where it is made available.

Our state has pioneered in ways to decrease mental disorders requiring hospitalization of older persons and has set up geriatric treatment units in its hospitals. The relationship between state hospitals and outside agencies is not sufficiently well integrated; facilitation of flow of patients between them is desirable.

It has been demonstrated that many mentally disordered older persons can be well cared for outside mental hospitals. However, there is a dearth of skilled persons and of facilities. Training persons to care for the aged ill must come first.

Disturbed behavior in the aged is a symptom of distress and not always a sign of deterioration or permanent disability. Psychiatric disorder in older persons may respond to psychotherapy, as well as to pharmacological and physical treatment.

All-around good medical care is an essential basis of the psychiatric approach.

Programs for the mentally disordered aged must be helped to evolve. Good care cannot be created by legislation. A hurried creation of programs and organizations may inadvertently prevent development of better ways of dealing with the problem.

Some Steps Toward Comprehensive Psychiatric Service. DR. PAUL H. HOCH.

The increase of mental patients in the state hospitals can be reduced only if we organize comprehensive psychiatric services. This would mean that we are in need of far more community psychiatric facilities, especially in the large cities, than are available today. It means that we would have to have more inpatient services in general hospitals and also an expansion of psychiatric clinics and day hospital facilities. The day hospital treatment will have to be studied. If this study should show advantages over full hospitalization, then a general application of such day hospitals will be in order. Through the Community Mental Health Act, the Department of Mental Hygiene is trying to stimulate inpatient facilities for psychiatric patients in general hospitals and the organization of psychiatric clinics. Later on there will be an attempt to establish a working relationship between the state hospital system and the psychiatric facilities in the community.

News and Comment

PERSONAL NEWS

Stanley Cobb Honored.—Dr. Stanley Cobb, for many years an editor for the ARCHIVES OF NEUROLOGY AND PSYCHIATRY, was honored on April 26, 1958, by the Boston City Hospital Alumni Association, who presented its General Leonard Wood Memorial Medal to him. Dr. Cobb was formerly head of the neurological service at Boston City Hospital, Bullard Professor of Neuropathology at Harvard, and head of the psychiatric service at Massachusetts General Hospital. He has also received the Albert Einstein award for outstanding achievement and the highest honor of the Association of American Physicians, the George M. Kober Medal.

Books

Introduzione alla elettroencefalografia clinica. By G. M. Corsino. Price, about $6.50 Pp. 195. L. Cappelli, Via Farini 6, Bologna, Italy, 1957.

This book is directed not only to the neurologist but also, and chiefly, to the general practitioner who uses electroencephalography in his practice. To this effect, an effort is made to present a "synthesis of the daily clinical situations in which the usefulness or necessity might arise to request an EEG examination" and "to furnish a minimum of theoretical and practical notions on the possibilities and limitations of the EEG technique." According to the author, the book should help the nonspecialist not only in interpreting the tracing but in understanding the EEG report, thus making possible the most profitable use of the latter in diagnostic and prognostic problems and in the selection of therapy.

Notwithstanding the modesty of intentions, the book is definitely the best of its kind ever to appear in the Italian literature and can be favorably compared with most of the monographs dealing with electroencephalography which have recently appeared in the international literature.

The book is divided into two main parts: In the first, theory, principles, and technique of electroencephalography are described. The various rhythms which can be seen in normal, as well as in pathological, conditions are outlined and discussed. Some brief notions on the anatomicophysiological substrate of the electrical activity of the brain are offered. The various methods of activation are enumerated, and their relative value is discussed; and, finally, some of the commonest artifacts are illustrated and described, as well as their most likely source of origin. A wealth of demonstrative tracings are included, and almost every single point made by the author in the text is illustrated by samples of typical EEG tracings.

In the second part, a number of clinical syndromes and their accompanying EEG patterns are presented and discussed. These include epilepsy, the EEG in children, intracranial expanding lesions, cerebral vascular pathology, head trauma, psychiatric conditions, and degenerative and inflammatory disease of the brain. Suggestions and general principles to follow in writing the final EEG report are given in the last chapter. The longest portion of this part is dedicated to the problem of the EEG in epilepsy. While the emphasis on convulsive disorders is justified and understandable, one may wonder why only three pages are dedicated to head trauma, and also why only three pages are dedicated to a chapter which includes psychiatry, degenerative disease of the brain, and various types of encephalitis and meningitis. Very likely this unevenness reflects the interest of the author and the patient material of the Neurological Clinic in Bologna; however, a book which is supposed to be an introduction to clinical electroencephalography is expected to provide an equal amount of information to investigators having different interests.

Many viewpoints concerning the anatomicophysiological mechanisms underlying the electrical activity of the brain are still hypothetical or highly debatable; yet the reader will have to look very carefully to find any reference to such problems. One cannot help admiring the almost dogmatic attitude of the author in these matters; yet the controversial nature of many such problems should not be so thoroughly ignored. In particular, the inexperienced reader should be made aware that different, though equally acceptable, interpretations or theories do, in fact, exist.

One of the merits of this book is in the number (117) and quality of the illustrations. The large majority of the EEG tracings are well chosen; almost all are technically satisfactory, and in over 90% the reviewer is in agreement with the interpretation offered by the author.

Few inaccuracies can be found in the text, and these are mostly related to technical questions; their presence does not lessen the value of the book. A minor, though regrettable, defect of the book may be found in the bibliographic references. A list of 149 quotations is given, but many of these do not appear in the text; on the other hand, several quotations which appear in the text do not have the corresponding reference. According to an explanatory footnote by the author, the bibliographical list should represent only those quotations having either a "historical" or a "highly scientific" significance. In the opinion of the reviewer, either the explanatory footnote or some of the names in the list should be deleted.

Cosimo Ajmone Marsan, M.D.

Chemotherapy and the Central Nervous System. By Henry McIlwain. Price, $10.00. Pp. 328, with 61 illustrations and 31 tables. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

In this volume the author, professor of biochemistry at the University of London, sets as his goal the development of two major themes: "firstly, the development of methods and principles in chemotherapy as a whole, and secondly, the application of chemotherapy to produce drugs for use in the treatment of mental disorders." This book, as did his last, "Biochemistry and the Central Nervous System," which appeared only three years ago, bears witness both to the thoroughness of his knowledge of chemistry and its neurobiologic applications and to the depths of his thinking in search for pattern and form among the diverse orders of this broad field, taking as his precept the idea "that chemotherapy can be regarded as an aspect of applied biology."

In brief, the book may be considered a search for basic principles in the chemotherapy of the nervous system as considered by a distinquished biochemist using an historical approach. The heart of the book is found in three chapters—two on the chemotherapeutic system, and the final chapter, entitled "The Nature and Results of Chemotherapeutic Trial." The former chapters are based on the concept of a chemotherapeutic system involving four components—the normal parts of the body, the abnormal parts of the body, the disturbing agent, and the drug and its metabolites. The first chapter is concerned with the bodily distribution and metabolism of drugs. In this the author deals at length with the distribution of drugs within the body as a whole, the access of the drugs to the central nervous system and their distribution there, and the bodily metabolism and disposition of drugs. The second considers the actions of drugs on the body and on the disturbing agent. The action of the drug and its metabolites on the normal body as a whole and on the central nervous system, and its actions on the disturbing agents and on the abnormal part are discussed.

In the last chapter, the author states in a more related form the basic concepts for which he has been searching throughout. He takes his ground here on Barcroft's proposition: "The fixity of the internal environment is in short the condition of mental activity." He finds "the relationship of chemotherapy to the central nervous system to be inherent in the reactions of the animal body to chemical substances." In a broad consideration of chemotherapy as a whole, the relationship between the therapeutic agent and the brain is an enduring theme. "From the local anaesthetics to the antibiotics and sulfonamides, central side effects and toxicity have conditioned the choice of agent."

During the last century of chemotherapeutic endeavor, compounds of natural origin have usually served as starting points in exemplifying therapeutic possibilities on the part of any chemical substances. Since this century has also been that of development of organic chemistry, this has led to development of huge series of chemically related agents produced in search of a more efficacious medicament. The author concludes, however, that "attempts to relate structure to pharmacological activity in organic compounds can usefully be made only among members of limited series of compounds." He stresses the progress to be made in accepting the "potential value in the central side effects incidental to chemotherapeuticals developed for other purposes" and stresses their exploitation.

Finally, he discerns that "among inventions of medical application, that of chemotherapy with substances whose synthesis has been guided by assay of chosen biological attributes, appears outstanding in the directness with which it replaces a random evolutionary process by a planned process of the same fundamental type. It replaces the random introduction of new substances resulting from mutations, by the introduction of chosen compounds to chosen individuals at chosen times."

In additional chapters the author discusses anesthetics, general depressants, antipyretics, antimicrobials, anticonvulsants, and analgesics. There are two very lucid chapters on chemotherapeutic agents used in nervous and mental disorders. In each of these chapters, the historical development of the medicaments is considered at length, along with efforts by chemists to develop more acceptable related compounds and their evaluation.

This is not a textbook of pharmacological therapy in neurological disorders but a personal approach to the problem based on a broad but selected basis. Unhappily, the book frequently appears to lack direction, and one wonders just where this is all leading, until the synthesis in the last chapter. Even in a book not intended as a general review, one may be disturbed by the inclusion of a scant two-page consideration of drugs useful in Parkinson's disease when compared with two long chapters on the agents active against infectious agents. Also, although

not specifically within the province of the book, one should have welcomed a consideration of replacement therapy on deficiency diseases involving the nervous system and a chapter on chemotherapy of the peripheral nervous system and the neuromuscular junction.

Still, there is no desire to cavil about minor points when considering a book of such all-round merit. Our thanks are due to Professor McIlwain for a book of such breadth and thoughtfulness that it will doubtless become a "must" for scholars in this field.

The book is well bound and printed, pleasingly illustrated, and remarkably free of typographical errors.

CHARLES E. WELLS, M.D.

Anatomies of Pain. By K. D. Keele. Price 27s. 6d. Pp. 206. Blackwell Scientific Publications, 24-25 Broad St., Oxford, England (American Agent—Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.), 1957.

Pain, disease, the mind, and the nervous system are the topics of this book. Beginning with the beliefs and customs of primitive and ancient peoples, the author achieves a broad historical synthesis by weaving the dominant theme of pain and its mechanisms into a background of evolving concepts of disease and nervous system function. While the large scope allows of frequent opportunity for discussion, qualification, and elaboration by the historical specialist, the broad outlines are undistorted. It is a fascinating story, a scholarly work, and a valuable addition to the library of those concerned with these topics.

The presentation of the contemporary period is the least lucid section of the book, reflecting perhaps the present lack of unanimity as regards even some of the fundamental concepts of pain mechanisms. For example, at about the same time that this book dealing with the anatomy of pain was published, a review article in a major neurological journal concluded that "a pain is always a pain, a quality like goodness or justice. Therefore there can be no pathways nor nerve endings for pain."

In his conclusions, the author selects three developments during the twentieth century that he considers to be of major significance as regards "anatomies of pain." The first of these is the "emergence of a second sensory system concerned with its [pain's] conduction." He links this to the reticular formation of the brain stem and suggests that it is of special significance for pain sensitivity. This has yet to be determined. The second of these developments is "the growing tendency to centralize the sensorium within the brain," as exemplified by the "visceral brain" of McLean and Fulton and the "centrencephalic integrative system" of Penfield. Such models are interpreted as indicating a renewal of the "search for the sensorium commune." This suggestion is charming for its flavor of historical continuity, but it is difficult to accept such models as major developments of the twentieth century, since the data on which they are based can be interpreted differently and they have so far met with only limited acceptance.

The third of these major developments, and the one with which the reviewer fully concurs, is "an increasing understanding of the biochemical aspects of sensation," in particular the opening of a "new and fertile field, the biochemistry of pain."

LORING F. CHAPMAN, Ph.D.

L'épilepsie. Etude clinique, diagnostique, physiopathogénique et thérapeutique. By J-A. Chavany. Price 2800 francs. Pp. 354, with 25 figures (17×25.5 cm.). Masson & Cie, 120 boulevard Saint-Germain, Paris, 6e, 1958.

This uncut, paper-bound volume provides a complete statement of contemporary views on epilepsy. It contains no new information, although the distinction between petit mal and minor seizures may be new to those who have graduated from medical school since 1945. The book is divided into four parts, the first of which describes the various types of epileptic seizure. The second portion describes certain special forms, such as epilepsy with mental disorders, reflex epilepsy, epilepsy in children, and nocturnal seizures. The third part contains a chapter on electroencephalography by G. Lobel. This is followed by chapters on differential diagnosis and etiological factors. The fourth part considers the pathophysiology of epilepsy and medical and surgical treatment. The work concludes with a chapter by D. Hagenmuller on medicosocial problems raised by epilepsy.

The work is considered excellent for French speaking students.

DONALD J. SIMONS, M.D.

Brain Tumors, Their Biology and Pathology. By K. J. Zülch: From Second German Edition by A. B. Rothballer and J. Olszewski. Price, $9.50. Pp. 320, with more than 100 illustrations. Springer Publishing Company, Inc., 44 E. 23d St., New York 10, 1957.

This volume is a succinct dissertation on the pathology of brain tumors, based on Dr. Zulch's analysis of 4000 personally examined cases.

The subject is approached systematically and fairly traditionally. The clinical expressions of intracranial neoplasms are largely omitted. The author employs a classification of brain tumor which is similar to, though not identical with, that of Bailey and Cushing. Clinical behavior is given more weight in biological evaluation than is histological appearance. After a historical review of previous classifications and the exposition of the present one, the general principles of brain neoplasia are set forth. There are short sections on causal theories of brain tumor, methods of spread, general and specific cellular characteristics, and the reaction of the brain to new growth. There follow individual sections on the detailed neuropathology, both gross and microscopic, of the various tumor subgroups.

The brevity of the volume has resulted in the omission of many intriguing aspects of brain tumors. The author omits discussions of pathological physiology, such as the mechanisms of the "brain swelling" and "brain edema" which occur with certain tumors. He describes in detail the tendency for certain neoplasms, such as the gliomas, to reside in certain geographical areas. However, there are no speculations as to why these distributions may occur or why certain tumors show a predilection for certain ages. Morphology receives almost the entire emphasis in this volume, and there is little attention given to the biochemistry of intracranial neoplasms. Admittedly, knowledge in this latter area is still fragmentary, but leads in this direction may eventually develop an effective chemotherapy.

The aforementioned omissions do not detract from the excellence of the presentation, however. Despite the author's apology for keeping the citation of other work to a minimum, there are 41 pages of bibliography. The translation by Drs. Rothballer and Olszewski is admirable, and the volume reads easily. The text is free from typographical errors, and the illustrations are of first quality. Since most other comprehensive English language works on tumor pathology are either out of date or out of print, this volume is well worth having.

FRED PLUM, M.D.

Hypothalamus und Thalamus. By W. R. Hess. Price, $8.60. Pp. 70. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N (American Zone). (American Agent—Grune & Stratton, Inc., 381 4th Ave., New York 16), 1956.

This atlas of documentary pictures with both German and English legends represents a succinct recapitulation of the investigations on the diencephalon conducted by Hess and his co-workers in the Physiological Institute of Zürich between 1924 and 1951. The accompanying text also is in both German and English.

The work was done on cats. The results of electrical stimulation and ablation are recorded by means of excellent photographs of the experimental animal. The site of the lesion is clearly indicated in sections of the brain, which are well oriented in key illustrations.

The book is divided into six sections, as follows:

I. The introduction, which contains key illustrations to the anatomy of the cat's brain, designed so that they can be used by other investigators.

II. Discussion of the autonomic effects and auxiliary somatomotor functions noted in the experiments. Observations are recorded on the following phenomena: pupillary reactions, panting, sniffing, rhythmic licking movements, and sleep and motor inhibition.

III. Description of the reactions of a compulsive character, such as affective defense reactions and bulimia, which were observed in some of the experiments.

IV. An account of the autonomic regulation of posture considered in connection with the mechanism for maintaining the normal posture of the head and body.

V. Observations on the following phenomena: (1) gaze movements following stimulation of the superior colliculi; (2) contraversive movements in relation to the forebrain, and (3) sensory representation in the orbital area of the cerebral hemisphere.

VI. Observations on the results of single and combined stimulation and the effects of radiation.

Each section consists of (1) photographs, with a brief description of the response observed; (2) a statement of the physiological significance of this response; (3) reference to the region stimulated; (4) the corresponding sections of the brain on which the points of stimulation are indicated, and (5) the author's publications bearing on this topic.

The author was able to correlate specific autonomic functions with certain circumscribed regions of the diencephalon, such as the hypothalamus, the preoptic and supraoptic areas, and the septum pellucidum. In no case, however, was sharp delimitation possible. On the contrary, there was overlapping of various systems. This is in keeping with the observations of other investigators on localization of function in the central nervous system. It is becoming increasingly evident that there are no centers in the nervous system, but levels of integration. A given function is represented at many levels of the nervous system and is dominant in some.

This work is an excellent reference book for the neuroanatomist, neurophysiologist, and neurologist. Its value is further enhanced by a list of 16 mm. films, copies of which can be obtained at cost from the Physiological Institute, Zürich.

LOUIS HAUSMAN, M.D.

BOOK REVIEWS

Die neuroallergischen Beziehungen in der Histopathologie der multiplen Sklerose. By Tibor Lehoczky. Price not given. Pp. 176, with 209 illustrations. Berlin, Akademie-Verlag, Berlin, W8, Mohrenstrasse 39, 1957.

This lavishly illustrated monograph is based upon a minute study of 20 autopsies on multiple sclerosis, with copious references to the literature. The author emphasizes the histopathologic findings in his cases in relation to experimental neuroallergy. He finds thromboses and hemorrhages in a minority of cases and considers them secondary or symptomatic. On the other hand, the perivascular infiltrations occurring both at the periphery of lesions and at a distance are commoner, and are believed to be primary and not merely symptomatic. The material does not permit positive opinion as to whether the demyelination or the inflammation comes first, but the infiltrations, as well as the formation of microgranulomas, appear to be an integral part of the process.

The disease process is a continuing one, as can be shown by the presence of acute and subacute lesions at the periphery of some of the sclerotic patches, even though the beginning of the disorder may date back 30 years.

The brunt of the attack by the agent falls upon the myelin, sparing nerve cells and axis cylinders within the focus. However, there are areas of perivascular and perifocal tissue edema and spongiosity or motheaten areas that represent swollen myelin sheaths and oligodendroglia, which the author believes are part and parcel of the allergic process.

It is somewhat discouraging to realize that once the multiple sclerotic process has started it seems to keep going, with the possibility of lighting up even after decades. The remarkable thing is that healed lesions are so seldom discovered as incidental findings at necropsy. Possibly routine examination of the visual pathways would yield some data along these lines, since they are so frequently involved (chiasma, 55%; nerve or tract, 45%, lateral geniculate body, 25%; periventricular white matter, 85%) in Lehoczky's material.

The author differentiates three stages in the sclerotic process: 1. Initial, consisting of perivascular rarefaction of the parenchyma at a distance from foci, with necrobiosis, which goes on to liquefaction of the microlesions. 2. The latent stage, which is appreciated only clinically but may last for years or even decades. (Retrobulbar neuritis patients are the best examples. More of them should be examined when death is due to other causes.) 3. Demyelination stage, the final stage, which gives the classical picture.

This handsome volume brings a method and an idea together in an effort to solve a knotty problem, the nature of multiple sclerosis.

WALTER FREEMAN, M.D.

A Textbook of Clinical Neurology. By Israel Wechsler, M.D. Eighth Edition. Price, $11.00. Pp. 782. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia, 1958.

The popularity of this textbook can be adduced by the appearance of an eighth edition. The general format of this new edition is similar to that of the previous one and includes a chapter on psychological testing by the author's brother, David Wechsler, and one on the

neuroses. The illustrations are good and the chapters arranged in a logical fashion. One wonders, however, whether it is reasonable to refer to aneurysms as slow-growing vascular tumors and to discuss them in the section on tumors of the brain. It is further confusing that subarachnoid hemorrhage is dealt with later. Although recent advances in neurology are, in general, adequately dealt with, a one-line reference to the possible role of abnormal copper metabolism in hepatolenticular degeneration is disappointing. Most confusing is the mention of the presence of a Kayser-Fleischer ring in pseudosclerosis of Westphal, whereas this sign is not mentioned in dealing with physical signs in hepatolenticular degeneration.

The well-chosen references to the literature of each chapter, the introduction to the history of neurology, and the comments from Dr. Wechsler's personal experience as a clinician are instructive and interesting.

Louis Hurwitz, M.D.

Autoscopic Phenomena

N. LUKIANOWICZ, M.D., D.P.M., Barrow Hospital, near Bristol, England

Introduction

The perplexing experience of autoscopy, i. e., of seeing one's own "self," or one's "double," has always puzzled and fascinated the human imagination and has been known to all races from time immemorial. The belief in the "double" may be found in the folklore of most nations, and it still persists in the mythology of some primitive societies. For example, some aborigines of Central Australia believe that after death their soul joins their double in the ancestral cave, where it is reborn (Róheim [79]). Dewhurst [22] regards the double "as an integral part of the brooding spirit of primitive man," and, together with Todd (Todd and Dewhurst [83]), assumes that it "is in the nature of a psychical atavism," and represents a characteristic feature of archetypal thinking.

The first report on autoscopy (about a man who could not go for a walk without seeing his double coming toward him) is attributed to Aristotle. Although the romantic theme of the double appeared in numerous literary works of the 18th and 19th centuries, it was introduced into medical literature only toward the end of the last century by Wigan (cited by Lhermitte [49]), whose patient could see and summon his double at his will. Most papers on autoscopy have been published by Continental writers, and only recently has this phenomenon begun to attract attention in the United Kingdom and in the United States. However, as there are still very few original cases described in the English language, it is thought worth while to give a brief account of autoscopic experiences in a few personally studied patients.

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Definition

Critchley [20] defined autoscopy as "delusional dislocation of the body-image into the visual sphere"; Lippman,[52] as "hallucinations of physical duality." Literally, autoscopy means "seeing" oneself in the visual space, as if it were one's image reflected in a mirror. Yet none of these definitions comprises all modes of perception usually involved in autoscopy, which is an intricate experience, including, apart from sensorial, emotional and cognitive "perceptions": The subject does not only "see" a true image of himself (visual perception); he may occasionally "hear" his specter "with his mind," though not with his ears (pseudoauditory perception); he also perceives the position in space and all apparent movements of the hallucinated phantom as his own movements (kinesthetic perception); finally, he is usually aware intellectually and emotionally of his double as of an integral part of himself (psychoemotional perception).

I should like to suggest the following definition: Autoscopy is a complex psychosensorial hallucinatory perception of one's own body image projected into the external visual space.

Report of Cases

Case A.—Mrs. A., a retired school teacher, aged 56, had experienced autoscopic hallucinations since her husband's funeral. When she returned home from the cemetery and opened the door to her bedroom, she immediately became aware of the presence of somebody else in the room. In the twilight of the late afternoon she noticed a lady in front of her. Mrs. A. lifted her right hand to turn on the light. The strange lady made the same movement with her left hand, and thus their hands met. Mrs. A. felt cold in her right hand and experienced a sensation as if all blood ran out of her hand. Under the electric light she noticed that the stranger wore an exact replica of her own coat, hat, and veil. In spite of this unusual situation, Mrs. A. was neither surprised nor afraid. She "felt deprived of any feeling," and, without bothering any more about the intruder, she began to undress and took off her veil, her hat, and her coat. The lady in black did exactly the same. Only then looking into the stranger's face, did Mrs. A. become aware that it was she herself staring at herself, as if in a mirror, and mimicking her own movements and gestures. It occurred to her that it was her "double," her "second self," looking at her. She felt that it was more alive and warm than she was herself. Feeling extremely tired and weary, she lay down on her bed. As soon as she closed her eyes, she lost the sight of her apparition. Almost at once she felt stronger, as if "the life of this astral body" was coming back into her own body. Soon she was fit to get up, to change her dress, and later to have her supper.

Since that evening she had been visited almost daily by her "astral body," as she used to call it, mostly at dusk, when she was on her own. She would see it only when she looked straight, and would lose sight of it as soon as she turned her gaze sideward or up or down. She would also make her double disappear by closing her eyes, but it would reappear after a while. Then, with her eyes closed, Mrs. A. would "see" her phantom just in front of herself with its eyes closed. Yet the double would open its eyes again as soon as Mrs. A. opened hers. The image was life-sized. The most distinct part of it was its face, torso, and hands; the lower part of the trunk and the legs were less sharply delineated. They were rather "misty" and "as if they were transparent." Yet the patient "knew and felt" the exact position in space of the phantom's legs at any time (kinesthetic perception). Soon she noticed that whenever she experienced her autoscopic hallucination, she "felt mildly amazed and bewildered" and had "a perplexing feeling of unreality."

The patient showed a somewhat peculiar "insight" (which is best illustrated by her own description): "In a detached intellectual way I am fully aware that my 'double' is only an hallucination. Yet I see it; I hear it; I feel it with all my senses. Emotionally, I feel it as a living, integral part of myself, as a materialized form of my own 'astral body.' It is me, split and divided. . . . O, doctor, it is all so confusing. And worst of all, I can't talk about it to anybody but to you, because everybody else would think that I am mad."

The only child of a high-court judge, the patient was of a rigid, mildly obsessional, and worrying type of personality, with a tendency to depressive moods. She retired at 48 because of a "nervous breakdown" (involutional depression?). At 26 she married a barrister aged 41. Theirs was a happy, but childless, marriage. Her husband died of coronary thrombosis at age 66. Ever since his death Mrs. A. had experienced her autoscopic hallucinations.

Case B.—Mr. B., aged 38, an architect, separated from his wife, had had an artificial limb since 1919, when, at the age of 25, his right leg was amputated just above the knee, after complete destruction of the knee joint by a grenade. Eight years later he developed epileptic attacks, preceded by a sensory aura in the form of excruciating pain in his nonexisting limb. In this respect he resembles the interesting case of Cohen,[9] whose patient referred his cardiac pain of coronary occlusion to his left (phantom) arm. The fits were diurnal in type and occurred at about 11 a. m. Thanks to their unusual regularity, the patient was able to organize his life so as not to be socially embarrassed or endangered by his fits.

He experienced his first autoscopic hallucination five years after the onset of his epilepsy. Sitting in his study and discussing some plans with his builder-contractor, he suddenly felt "very sad and weary." He stopped talking and turned his head to the door leading into his study. There he saw a tall man, dressed in a replica of his own suit, wearing a monocle in his right eye (which Mr. B. wore at that particular moment), come, like a "semitransparent mass," through the closed door and slowly approach his desk. "The phantom was absolutely identical with me," reported B. later, "but for one detail: It did not show the slight limp I always have because of my prosthesis." As the apparition approached the desk, Mr. B. "felt like paralyzed. I could not move. I felt as if all my life left my body and went into him." Then he apparently lost consciousness, though only for a few seconds, and no motor phenomena were observed by the builder sitting across the table. All he noticed was an unusual pallor on his employer's face and a vacant expression. Here is the builder's verbatim report: "When I asked Mr. B. if he did not feel well, he did not answer. He was staring

at the door and seemed not to hear me. After a second or two he got up, walked to the door, and tried the handle. He then came back to his desk, looked at me, and said: 'Yes, Mr. P. Where were we? O, yes, I know,' and he carried on with his explanations just from the very point where he had stopped a minute ago. Yet he was not in his usual form: He had difficulties in expressing himself and, after a minute or two, broke off altogether, asking me to call again later. I could see that he was not at all well and that he wanted to get rid of me."

The patient gave this retrospective account of the events: "I and my double melted together into one body and one soul. Everything became at once so lifeless, empty, and meaningless, so unreal, and so far away. I do not know how long it lasted, but it seemed ages to me. Finally, 'he' left my body again, and I saw him walking slowly toward the door. On this occasion he was limping on his right leg, as I always do, and somehow I knew that he felt tired and weary. He disappeared through the closed door, without opening it. Then suddenly I felt an irresistible urge to go over to the door and to satisfy myself that it was really closed. I do not know why I did it. It was like carrying out a posthypnotic command. After this experience I felt weary and tired, and much older. I had difficulties in finding the right words and could not continue to discuss the technical points with my contractor. So I sent him away, and, as I felt headachy and sleepy, I went to my bedroom and lay down. I fell asleep, but woke up in a little while feeling fresh and fit again."

Mr. B. had altogether five such experiences, all of them in his study, all at the same time of day, almost exactly at 11 a. m. (he used to point out that this was the time when he had lost his leg in battle). After his fifth autoscopic incident, the patient became alarmed. He kept thinking of Maupassant's "La Horla," and was afraid that he himself was "getting mad." He went to Vienna, accompanied by his sister, to consult Professor Poetzl. On his arrival at the Staats-Bahnhof in Vienna, Mr. B. walked straight onto an oncoming electric tramcar, before his sister could grab and stop him. He was killed on the spot. According to his sister, "he was though in a trance and absolutely oblivious of his environment."

The patient's maternal grandfather committed suicide at age 62. His mother suffered from migraine. She died in childbirth, when the patient was 4 years old. He was the youngest one of four siblings. The patient's father remarried, and the children were brought up by their stepmother. B. had a happy childhood, with the usual milestones and no neurotic traits. He was a brilliant student, and qualified in architecture in Vienna. In personality he was extroverted and sociable—a typical *bon vivant*.

Case C.—Mr. C., single, aged 55, a machine operator, had experienced autoscopic hallucinations for about eight years. He said that at almost any time, particularly at dusk, he would see "my own image, as if reflected in a mirror, just in front of me, conducting an orchestra or a jazz band." The phantom was life-sized. It was always dressed in an exact replica of the suit the patient was wearing and had his very features ("just like my photo") and his facial expression. Mr. C. had no doubts about the identity of the specter: "It is me, all right." He would see the apparition either in profile or half-turned to him. He never actually saw the orchestra, but had what he called a mental picture of it, and could hear in his mind the music they played.

He had also a different, more frequently met, kind of autoscopic hallucinations, when he would see only his face, sad and distressed, right in front of him, about a yard away. Besides actually "seeing" it, he experienced an emotional and kinesthetic sensation, a feeling of unity and oneness with it, as well as a mental notion that this was his own face, a part of himself, or "the face of my double," as he used to call it. He would see this face many times a day; e. g., he saw it several times during his first interview on his admission to hospital. It had the physical "solidity," and even "the dusky complexion," of his own real face, although he did not actually hallucinate it in color.

Apart from autoscopic hallucinations, Mr. C. experienced another, less common, type of hallucinations of a synesthetic nature, which he tried to describe in these words: "You would see little people with shrieking voices in your ears." (?) Unfortunately, he was extremely reluctant to discuss or elucidate this point any further, being afraid that he might be regarded as "mental." All assurances and endeavors to dispel his fears failed to make him more communicative. (This unusual reluctance to reveal the hallucinatory experiences was noticed also by Dewhurst.) Mr. C., like Mrs. A., showed a peculiar "insight" into his condition: He knew that his experiences were "unreal," in the sense that other people could not experience them as he did; yet, at the same time, he felt that they were "real enough to me personally."

This patient was admitted to hospital because of a *depression* of about 10 years' duration. This preceded his autoscopic experiences by approximately two years. It seemed to have been precipitated by his knowledge that he was suffering from sarcoidosis of the skin, which had also infiltrated internal organs (e. g., his lungs). The illness necessitated an almost total amputation of his penis two years prior to his admission. There

was no family history of morbidity, and Mr. C. himself was always a good mixer and of a "happy-go-lucky" disposition before his present illness. However, when the sarcoidosis of his face became more pronounced, he became extremely self-conscious, developed a mildly paranoid attitude toward his environment, and began to avoid people. He became more depressed and more anthrophobic after the peotomy.

Five electric convulsive treatments resulted not only in a complete remission of his depression and of his ideas of reference but also in a full disappearance of his autoscopic hallucinations. A follow-up study over a period of almost two years did not show the recurrence of his depression or of his autoscopic experiences. This patient seems to be the only known case of autoscopic hallucinations who was cured of his autoscopy by a physical method of treatment.

Case D.—D., single, aged 32, an electrical engineer, had become subject to autoscopic hallucinations in the last 18 months, seeing an image of his own face "as if looking at it in a mirror." This phantom face would imitate all his facial expressions and D. would frequently "play with it," forcing it to copy his mimicking. The patient's attitude toward his double was overtly sadistic, although he regarded the apparition as a part of himself. For instance, he would often strike the phantom on its head, and the specter was not able to avoid the blows. It had to remain in front of D., always just within the reach of his arm (in contrast to all other known cases).

D. gave the following description of his visual experience: The phantom's face is life-sized. It is gray, "like a photograph." It is most distinct in its center; toward the periphery it turns misty, and its contours are less sharply delineated. Its texture is not transparent but also not solid; "it looks soft, like a jellyfish." Although D. can touch the specter, he experiences no tactile sensation in his fingers. The phantom-face is almost continually on the fringe of awareness, though the patient does not seem to be conscious of it all the time. However, as soon as he begins to think of it, he can see it immediately. It may appear anywhere and in any circumstances—in company, as well as when he is alone. D. has also auditory experiences: He stated that he can often "hear" his double "in my head and in my mind." (He also sometimes hears "some other voices," but they "are different from the voice of my other me."

D. is a solitary, chronic, withdrawn schizophrenic, who often grimaces and appears to be almost continually visually and aurally hallucinated. His father, a habitual drunkard, was invalided from the Army after the First World War with 80% disability for "shell shock." He had been in and out of mental hospitals ever since. The patient's brother was also treated in this hospital on two occasions for an "anxiety reaction in a hysterical and psychopathic (?) personality."

Case E.—E., a man, single, aged 26, a road sweeper, saw his "double" four times, at approximately yearly intervals, when he was sleeping alone in a small side-room, always at the same time of the early morning (about 4 a. m.). In his sleep E. felt as though something forced him to wake up and to look straight to the door. There he would see his own face gazing steadily at him. Here is an excerpt from his written report: "First of all, you see a white mist in the center and then, after a few minutes, you see yourself, your own face, as if in a mirror. You are in a brown jacket with a bright-red collar around your neck. Then you see your right arm going up, and your hand going white. And then you see your face getting whitish-gray and disappear in mist." On each occasion the apparition stood exactly in the same place, in the doorway, looking straight at Mr. E. (A similar constancy of time and place was also characteristic of the double of Mr. B.)

The autoscopic experience in this case was only visual, and there were no affective ties between this emotionally blunted schizophrenic and his double, although the patient was aware of his vision as of a part of himself. Because of E.'s mental condition, it was difficult to obtain any more information or spontaneous description. On the other hand, every endeavor was made to avoid any trace of suggestion in our questions.

The patient's family history was clear. His premorbid personality was described by his mother thus: He was always "a very good boy, shy, very quiet; kept himself to himself." He was never interested in sports, games, dances or the opposite sex.

Case F.—Mr. F., single, aged 23, a confectioner's apprentice, an epileptic, had experienced autoscopic hallucinations four or five times during the past two years. His epileptic attacks were ushered in by a combined visual (stars and flashes of light) and "psychic" (some obsessive phrases and irritability) aura. After that he would have one of the following attacks: 1. A typical grand mal seizure, followed by a short-lived confusional episode, with clouded consciousness and automatic wandering. 2. A confusional state, which on such occasions seemed to be itself a seizure-equivalent. This often lasted two or three hours and resembled a short-lived epileptic fugue: The patient would usually go on an aimless bus ride, taking and changing buses several times in a haphazard way. 3. F. might pass from his visual aura into an intricate state of autoscopic hallucinations, associated with a very short confusional state and concluded by his usual compulsory wandering.

His autoscopic experiences were always preceded by a distressing feeling of unreality.

Mr. F.'s verbatim account follows: "I always know when I am going to have this 'turn.' A moment or two after I cease seeing my flashes and stars, I feel very queer: Everything seems to be so far away, so unimportant, so odd, and so unreal. I don't feel 'myself' anymore. I feel dazed and 'empty' in myself. My body is like an empty shell. Then, all at once, I see and feel how my 'shadow,' or 'my other me,' steps out of me, of my earthly body. He makes two or three steps, then stops, and turns his head to me. I feel how my soul and my life leave my body and enter him. Soon *he* is the real me, and what is left of the 'old' me is only 'my outer body,' just like an empty shell after the chick has hatched. Then he nods at me and begins to walk, and my empty body follows him like a shadow. Often he walks right through a shut door, but my 'real' body can't do it." (The patient's brother reported that on more than one occasion he saw F. trying to walk through a closed door, knocking himself at the panel.) "I have to follow him blindly, till my empty body can seize him again into itself, just as you catch the yolk into an empty half-shell. Only then I feel my old self again, and can think and feel once more. Usually I feel tired after that and have a headache; so I know that I have just had my odd turn."

F. described his double thus: "He is like a photograph, or like old films, with no color at all." The specter is semitransparent: "I can almost see through him, like through fog or mist." The patient sees the face of his double "just after he gets out of me and stops in front of me. It is so strange: He looks at me, and I look at him, and I can see that his face is my own face, as if I would be looking at it into a mirror. I see his face once again, just before the chase is over. Then he again stops in front of me, about a yard away, and waits, as if tired of this pursuit. He turns his face to me and nods, as if saying: 'Come on and get me.' In fact, I can hear him saying that, though really I hear it with my mind, and not with my ears."

F. was the youngest of five siblings. There was no family history of morbidity. He had the common childhood illnesses and typhoid and malaria during the War. The first attack of epilepsy (grand mal) occurred aboard the ship taking him and his brother from Russia to Persia in 1942 (he was then 13). He had no more fits for the next five years, but lately they recurred, at irregular intervals, three to six fits a year. He began to experience his autoscopic hallucinations in 1950 and had four or five "turns" in the last two years. He was a conscientious, hard-working, meticulous man, very particular in dressing. He made friends easily and liked films, music, dancing, and races. He had a girl friend, and planned to marry her. In the meantime, he lived with his married brother.

CASE G.—G., single, aged 20, an accountant's clerk, had begun to see his double over two years before. He usually saw only the head and the bust of his apparition ("it is like a portrait or a photograph of myself"), but occasionally "the whole picture, full-sized." The double was always dressed in an exact replica of the suit the patient was actually wearing. G. saw his double "in all natural colors." The phantom remained in front of him indefinitely long, usually about a yard or so away. G. could make him disappear by closing his eyes or by looking sidewise, but as soon as he looked again straight in front of himself, the "other self" was inevitably there. Usually the double imitated the patient's facial movements, but occasionally G. succeeded in outpacing his double by changing his facial expressions so quickly that his "other me" could not keep up. Sometimes the double's facial expression might remain unchanged in such circumstances, and it might look at its "original" with disapproval and dismay. (The patient's spontaneous comment at this point was: "It's like my own conscience trying to put me right.")

There was one peculiar feature about G.: He was the only patient in this series who talked about his visual experiences quite freely and without reluctance. He even agreed to some experiments on his double: 1. When a solid object, e. g., a book, a sheet of paper, or a brief case, was placed "between" the hallucinated double and the hallucinating patient, the latter would claim not to see his phantom any more. 2. When the same solid object was placed "behind" the double, the patient alleged that the double obscured the given object, and after a while G. could see only his double, but not the solid object "behind" it. Unfortunately, when further experiments were attempted, the double seemed to have become "annoyed" and disappeared for a while altogether. (This property of G.'s double to eclipse or make invisible other objects resembles a similar property ascribed to apparitions [Tyrrell[96]].)

Besides visual hallucinations, G. experienced auditory ("autophonic") hallucinations: "I can hear him speaking to me, although it is rather difficult to explain it. It's like hearing my own thoughts, yet not quite, because I can think and talk about something different, while he keeps talking to me about something else." Although the patient emotionally feels his double as an integral part of himself, he shows a disparaging attitude toward him: "My second self is only a copycat. He has no original movements or ideas of his own, apart from the occasions when he scolds me."

The patient developed his schizophrenic symptoms at age 15 ("I felt then that I lost all my emotions. For instance, I could neither cry nor feel sorry when my mother died.") He often experienced feelings of unreality and was subject to visual hallucinations, at first of a crude type, such as flashes of light, and later "white bars, wavy lines, hexagonal nets," and other simple geometrical patterns. In this respect there is a striking likeness to mescaline hallucinations (Klüver[16]; Maclay and Guttman[14]; Mayer-Gross[17]; Smythies[18]) and to hypnagogic imagery (Leaning[11]; McKellar and Simpson[13]). In spite of his hallucinations, G. succeeded in taking his G. C. E. and obtaining employment as an accountant's clerk. At 18 he joined the R. A. F., but soon afterward his symptoms became worse. He began to hear "voices," and his visual hallucinations became more highly organized: He began to see human faces, a resemblance to the "faces-in-the-dark phenomenon," encountered in hypnagogic imagery (Ardis and McKellar[5]). Soon the patient became disturbed and confused, and he only vaguely remembers that he had ECT and a "short course of modified (?) insulin," after which he was discharged from the R. A. F. as medically unfit. He went back to his civilian clerical job, but relapsed within one year and was admitted to the Barrow Hospital in June, 1957. After a full course of insulin coma therapy, he was discharged symptom-free and was able to resume his employment. He was seen twice at the follow-up clinic. He remained free of schizophrenic symptoms but continued to hallucinate his double.

His father, aged 53, had been treated in this hospital for Jakob-Creutzfeldt disease. His mother, who was a Lesbian, died at 42.

Comment

The double usually appears suddenly and without any warning, but in epileptic and migraine patients there may be a brief sensory aura just prior to the appearance of the double. In such cases the autoscopic experience itself seems to be an "equivalent" of the epileptic or migraine attack. (For instance, the autoscopic hallucinations of Mrs. A., as well as those of two epileptic patients, B. and F., were preceded by an acute feeling of unreality, resembling the attacks of depersonalization in a 17-year-old epileptic girl described by Todd and Dewhurst.)

Most frequently, the subject sees "only the head, the bust, or, more rarely, the whole figure" of his double (Conrad[17]). There is a striking resemblance between such anatomically incomplete doubles and the "faces in the dark phenomenon" found in hypnagogic hallucinations. Three of our patients (B., C., and F.) usually saw the whole figure of their specter; the four remaining patients mostly saw only the face of their double.

The phantom, in particular its face, is usually seen clearly and in sharp outlines, sometimes even with minute details. In this respect there is again a similarity to hypnagogic imagery, with its "microscopic clearness of detail" (Leaning), as well as to the unusual clearness of particulars met in some apparitions (Tyrrell).

The color of the double is described by subjects as being "gray" or "misty." The apparition is very exceptionally seen in color; yet two of the present patients (E. and G.) claimed to have seen their respective doubles polychromatically. Also, one of Dewhurst's patients experienced a colored autoscopic vision.

The texture of the double may be manifold: Sometimes it appears to be transparent, so that the subject can see through it (e. g., Patient A.); more frequently it looks semitransparent, being compared to mist or fog (e. g., Patient F.); occasionally it looks "jelly-like" (Patient D.); in Case G. the texture of the double was so solid that it eclipsed everything "behind" it. Yet, in spite of the solidity of its texture, neither this double nor any other in the present series cast a shadow. (This seems to be a differential feature between an autoscopic double and an "apparition," which, according to Tyrrell, usually throws a shadow.) Similar qualities of texture, i. e., transparency or semitransparency, may be attributed to solid objects under the influence of mescaline. (For example, an ordinary wooden table appeared to be semitransparent to Blackburn[8] after he had taken mescaline.) Also, the "self-apparition" of Archbishop Frederic seemed to him to be transparent, and he could see

through it and identify some books lying on a table "behind" it (Tyrrell).

The autoscopic double usually copies all movements and facial expressions of its "original," resembling a patient with echopraxia (e. g., our Patients D. and G. and Wigan's patient). The movements are copied in a "mirror-writing" fashion; i. e., when the subject lifts his right hand, his double lifts its left hand, exactly as would be the case with the subject's own reflection in a mirror (Case A.).

Almost all our patients perceived their double multisensorially. In addition to "seeing" their phantom, they also "heard" it, as well as "felt" it kinesthetically and emotionally as an integral part of themselves. For example, Mrs. A. at first "felt" the presence of somebody else in the room before actually "seeing" her apparition. In this respect she resembled the patients of Critchley[21] with organic brain lesions, as well as a female patient of Todd and Dewhurst. Only in one case (Mr. E.) was the perception confined solely to the sense of vision.

The subject's emotional reaction to his double may be a diverse one: Most frequently it is one of sadness (e. g., Cases A. and B.), less often one of amazement (Cases D. and G.); in rare instances the patient remains emotionally indifferent toward his experience (Patient E.) or shows an overt narcissistic satisfaction on seeing his double (Mr. C.). The emotional reaction to his double on the part of Patient F. was difficult to assess, owing to his postictal confusion, but there was something of the oriental fatalism in his attitude toward his "other me," some obsessional rush, some morbid urgency, some catastrophic unavoidability, as in a classic Greek tragedy.

The sensory feeling attributed by the subject to his double, or his "other self," is usually one of coldness and weariness. It is interesting to note that the sensory feeling one is supposed to experience in the presence of a "ghost" is exactly the same, i. e., one of coldness, described by the subject often as a "breeze of cold air" blowing from the apparition (Tyrrell, and also Martin.[55]). On such occasions, also, the patient's real body usually feels cold, and somehow lifeless, behaving like an automaton (e. g., Patients B. and F.). Less frequently "the other self," or the "astral body," may appear to be the more alive and more real of the two. (That was the case with Patient F. Also, Mrs. A. felt that her double was "more alive and warmer" than she was herself. The epileptic patient of Todd and Dewhurst already mentioned, felt that her "invisible double" seemed to "contain her mind.")

The subject remains aware of his psychophysical identity and of his actual, "real" body, as well as of its position in space throughout the whole experience and seems to be conscious "at the back of his mind" of the unreality of his experience. This peculiar detached "insight" in autoscopy is entirely different from the attitude shown by a hallucinating psychotic patient, who has an unshakable belief in the reality of his experience; it is also unlike the critical insight of a hallucinating organic patient, who is mostly aware of the unreal character of his vision. (An interesting illustration of the latter condition is to be found in a patient of Pick's,[69-71] a man of 62, with a right homonymous hemianopsia resulting from several apoplectic seizures. He once saw a dog on his right side; at another time he saw a girl with a colored shawl on her head, also on his right side; yet on each occasion he knew that his visual experience was not real). Thus, the insight in autoscopy lies somewhere between a complete acceptance and a complete rejection of the reality of the hallucinated phenomena. It resembles the "very private" notion on the part of some children of the make-believe nature of their "imaginary companions" (Bender and Vogel[7]).

In patients with temporal-lobe tumor causing hemianopsia the hallucinated phenomena are "seen" in the blind field of

vision (Fuchs[27]; cases of Horrax[37] and of Pick). In cases of autoscopy the localization of the double may be various: 1. Most frequently the phantom appears in the visual space straight in front of the subject, usually only about 1 yd. away, yet just beyond the reach of his arm. (Patient D. in the present series presents a rare exception to this rule.) 2. Less often there is no particular spatial correlation between the double and the body of the hallucinating patient (cases of Sollier,[91] Sivadon,[87] and Lhermitte[48,49]). 3. In epileptic and migraine patients there seems to be often a very odd, peculiar to each patient, spatial relationship between the subject and his double (Lippman).

This complex experience of physical, emotional, and psychical duality lasts usually a few seconds only. Nevertheless, since the patient's appreciation of time is impaired, the duration of the autoscopic state often appears to him to have lasted "for ages" (e. g., Cases B. and F.), contrary to the memory disturbance met in the phenomenon of "panoramic memory." This sometimes occurs in the temporal-lobe syndrome but has been claimed also by people unexpectedly exposed to extreme mental stress connected with imminent death, e. g., in men who faced a firing squad, in fliers who parachuted from shot-down or burning airplanes, and in persons saved in the process of drowning. A common denominator in all these conditions might be the impairment of time perception precipitated by a complete emotional "paralysis" and the filling-up of the total awareness with a passive watching of some experiences, or events, utterly beyond the patient's control.

According to Leaning, the frequency of occurrence of hypnagogic phenomena "varies between a single occurrence in a lifetime to the habitual seeing by day, whenever the eyes are closed, and by night, with the eyes open or shut." Likewise, there is no hard-and-fast rule as to the frequency of occurrence of autoscopic phenomena: 1. In many cases the double appears only once or twice in a patient's life, usually in poor illumination, precipitated by some emotional stress or physical exhaustion. (Some examples follow: Dewhurst reported the case of a doctor who saw his double before dawn while he was on a solitary walking tour. Sivadon's patient, also a physician, met his double on his way to the hospital on a cold morning, when he was shivering from influenza. Also Patient A., in our series, felt tired, exhausted, and mildly depressed when she saw her double for the first time. Significantly, also, Archbishop Frederic saw his "self-apparition" when he arrived home tired and fell asleep.) 2. In other cases the double may be perceived continually, following the original body like a shadow, being almost all the time on the fringe of the patient's awareness (e. g., in Case C. and also in Conrad's case). 3. In cases of epilepsy autoscopic episodes may occur at more or less periodical intervals, provided the fits themselves show some periodicity: (*a*) Most frequently the autoscopic experience takes place during the confusional period after the fit (Penfield's "postictal" type[68]), (*b*) less often it occurs as a visual aura before the fit ("preictal" type); (*c*) occasionally autoscopy may represent the epileptic fit itself ("ictal" type). The last type was experienced by our two epileptic patients, B. and F., who displayed also some signs of a "twilight attack" (Meyer-Mickeleit[62]), such as automatic, stereotyped behavior (i. e., in B., turning the handle of the door; in F., an aimless, compulsory wandering). In Case B. the whole autoscopic experience, which was identical with a "temporal lobe seizure" (Jasper[39,40]), was followed by transient dysphasia, tiredness, headache, and irresistible sleepiness, almost of a narcoleptic intensity. His transitory dysphasia was also suggestive of an irritative (vascular spasm ?) focus in the temporal lobe (Mayer-Gross, Slater, and Roth[59]). 4. In migraine, as in epilepsy, the autoscopic

experience may occur before, during, or after an attack of hemicranic headache. In some cases the autoscopic hallucinations have been known to precede the onset of the migraine pain by two to three days, "coming and going in flashes" (Lippman). At least in one of Lippman's cases the whole autoscopic experience seems to have been the equivalent of an attack of migraine.

Autoscopic phenomena may occur at any time of the day or night. Yet, apart from the relatively infrequent cases in which the double is present *all the time* (e. g., Cases C., D., and G.; also the blind patient of Conrad) or *almost all the time* (Case A.), or in which it may appear at *any time* (as in most of Lippman's cases), the great majority of reported patients usually saw their double either in the late evening or *at night* (e. g., the postencephalitic girl described by Lhermitte), or *at dawn* (e. g., Case E., and the patients of Sivadon and of Dewhurst). These times facilitate the appearance of any visual phenomena, as both the intrinsic factors (the anticipation and the apprehension on the part of the subject) and the extrinsic ones (twilight or a dim light) are highly conducive to visual misinterpretations, or even hallucinations, particularly in persons with a vivid visual phantasy (Goethe's romantic poem "Der Erlkönig"). Also, the survival of superstition, magic, myth, and folklore in our subconscious are partially responsible for this predominantly nocturnal character of autoscopy. Thus, for instance, superstition and folklore alike expect all unusual or "supernatural" phenomena to take place at night (e. g., "ghosts," as well as "The Evil One," are said to appear with the last stroke of the clock at midnight; likewise, the "witches" suppose to begin their activities only after sunset).

Although there seems to be a considerable preponderance in the number of female autoscopic cases reported in the psychiatric literature (the ratio of female to male patients being approximately 3:2), the significance of *sex* in the occurrence of autoscopic phenomena is not clear, and is probably of no particular relevance. It may even be an accidental factor. (For example, the sex ratio in the present material is 1 female to 6 males, a ratio which is easily explained by the fact that in the last 11 years I have been working almost exclusively with male patients.)

There also seems to be no correlation between autoscopy and *intelligence* or education. In the present series, two patients (A. and B.) had superior intelligence, a university education, and scientific degree; three patients (C., F., and G.) were of bright intelligence, and the remaining two (D. and E.) had a dull normal intelligence. All the last five had an education of the "modern secondary school" standard. Similarly, "eidetic cases are scattered, from the feebleminded to the superior adult" (Saltzman and Machover [81]).

It is impossible to establish the ages of all reported cases, as some authors (mostly French) fail to mention it, referring to their patients as "a young lady" or "a young girl" (Lhermitte). The mean age of patients reported by various writers was 39 years; in Lippman's material, it was 39½ years. The ages of our patients ranged from 20 to 56 years, the mean being 35 years 9 months. The factor of *age* does not appear to play any significant part in the etiology or phenomenology of autoscopic phenomena.

No relevant or reliable data regarding the *heredity* could be found in the great majority of cases described by various authors, except for Lippman, who stated that his reports "are confined to people who are free of neuropathic and psychopathic inheritance" (yet all but two of his patients had mothers suffering from "classic migraine attacks"). In the present series only Case E. had a morbid family history, and there was one suicide in the family of Case B. As far as it is permissible to draw conclusions from such incomplete data as we possess at present, it

seems that there is no noteworthy relationship between autoscopy and a morbid heredity.

No particular character traits could be elicited in the patients of this series which would suggest the existence of a particular "type of personality" especially prone "to react with" or "to develop" autoscopic hallucinations: Two of our patients (A. and F.) showed some obsessional perfectionistic features; one patient (C.), some narcissistic trends; B. was a typical extrovert, and the three schizophrenic patients (D., E., and G.) presented a shy, introverted, inclined-to-withdrawal type of personality.

According to Critchley,[19] "Heautoscopy has been encountered in a number of morbid conditions, including drug intoxications, delirium, hysteria, schizophrenia, and demoniacal possession." Yet there seems to be no significant correlation between various psychiatric disorders and autoscopy. For instance, in *schizophrenia*, with its proneness to various hallucinations, the autoscopy is an extremely rare occurrence. It is equally rare in the next most frequent psychological disorder, the group of *depressions*. (Although such factors as fatigue and exhaustion, which are connected with a depressive mood, appear to be conducive to autoscopic hallucinations, depression as a recognized psychiatric disorder seems to have no causal relationship to autoscopy.) Instead, there seems to exist some affinity between autoscopy and *epilepsy*, as well as *migraine*. In fact, most of the reported autoscopic phenomena seem to have occurred in subjects suffering either from epilepsy or from migraine. The character of this relationship is yet unknown, but it may to some extent depend on certain common psychological traits, such as the egocentric and narcissistic type of personality, combined with a vivid visual imagery). Temporal-lobe epilepsy, with its proneness to complex visual hallucinations, has a different, particular to itself, relationship to autoscopy.

The concomitant psychiatric conditions in the cases under review in this paper were depression, two cases; epilepsy, two cases, and schizophrenia, three cases. There seemed to be no etiological correlation between autoscopy and the coexisting psychiatric disorder in our patients.

Case C. seems to be the only one yet reported in which the autoscopic hallucinations were brought to an end by a physical method of treatment. The only similar case was that of a 55-year-old male patient of Pisetsky,[72,73] whose very painful phantom of both amputated legs and the accompanying depression disappeared (after more than five years' duration) in response to a course of ECT. In the present state of our knowledge, it seems that the most rational therapeutic approach would be to attempt to treat the basic, underlying condition, particularly in cases with a known organic etiology (e. g., temporal-lobe lesions), thus attempting to influence the autoscopy indirectly.

Autoscopy and Some Related Phenomena

Phenomenologically and psychodynamically, autoscopy is related to such complex parahallucinatory visual perceptions as imaginary companions, eidetic images, self-appearances, clairvoyance, hypnagogic imagery, and sleep hallucinosis, as well as to such anatomically incomplete phenomena as phantom limb and delusional reduplication of parts of the body. It has also a close affinity to certain highly elaborated visual phenomena of hallucinatory clearness and intensity met in temporal-lobe lesions. A brief survey of some of these phenomena follows.

Imaginary Companions.—They are mental images projected into the visual space and "seen" in the perceptual field by children deprived of love and affection. These phenomena are neither illusions nor hallucinations in the strict sense of the word. They are probably exteriorized wishful thoughts, psychodynamically identical with daydreams, and with wish-fulfilling dreams.

They have a compensatory character: By means of imaginary companions and his identification with them, the rejected (usually because of his, or her, "unwanted" sex) child can share in a vicarious way in the love and affection which his parents or their substitutes shed upon the imaginary companion (representing the sex desired by the child's rejecting parents). There is a resemblance to autoscopic experiences, in which the subject also "sees" his double in the visual space. Dynamically, these "companions" are akin to eidetic images, differing from them in being perceived as more "material" and more "real," although only of make-believe nature. The children concerned are, so to say, "privately" aware of the unreality of their experiences (cf. some children described by Bender and Vogel [7]), and their "insight" resembles the peculiar insight found in autoscopy and in eidetic imagery.

Eidetic Images.—There is a diversity of opinion in the appreciation of these phenomena. For instance, Urbantschitsch [95,96] regarded them as "subjective visual images," probably "memory images"; Jaensch [38] placed them halfway between memory images and after-images; Allport [2] preferred to see in them "a special variety of memory images." On the other hand, Crafts [18] regarded all these phenomena as different and independent. In his opinion, an eidetic image is externally projected, and actually "seen," being clearer and richer in detail than either the after-image or the memory image, which also persists longer and may be revived at will. Busse [14] saw in eidetic images "the ability to reproduce with sensory clearness a sensory impression after a shorter or longer interval." I should like to suggest the following definition: The eidetic image is a subjective visual experience of hallucinatory vividness and clearness, mostly met in children; it represents a projection (with apparent "seeing," i. e., with a visual sensory perception) of a mental image into the external perceptual visual space.

There are many similarities between the autoscopic and the eidetic phenomena. Thus, an eidetic image, like an autoscopic double, may appear either polychromatic (Cases E. and G.) or without chroma (as in most cases of this series and in all other known cases). Both phenomena are influenced with regard to their content by particular interests and various associative determinants, and both arise spontaneously and persist for an indefinite time. Further, as in autoscopy, there are no rules in the localization of an eidetic image: "Most persons see it in an indefinable sort of way; others see it in front of the eye; others at a distance corresponding to reality" (Galton [28]). The localization, the clarity of the picture, and its texture seem to be determined by the set and attitude of the subject; and, as in hypnagogic imagery, "as soon as this 'objective' attitude becomes ever so slightly critical, the localization ceases to be definite, the outlines become blurred, and the image is again essentially soft and insubstantial" (Braddock [11]). Some authors (e. g., Schilder [88]) have pointed out the structural similarity between eidetic images and hallucinations; others (e. g., O'Neill and Rauth [66]) have stressed the fact that, in contrast to hallucinations, the content of eidetic image is never confused with objective reality. The same holds true of autoscopic experiences.

The faculty of seeing eidetic images is most pronounced in children and, according to Jaensch,[38] recedes in adolescence. Allport explains this by the concretivistic thinking in children and their tendency "to project images if they are vivid enough, and complete enough, to simulate perceptual data" (Allport [2]). Jelliffe [41] assumes that "an atavistic trait may be involved in eidetic imagery," and that the ability to see eidetic images may represent a certain stage in psychical evolution. Similarly, Jaensch regards the eidetic imagery as a phase in normal psychological and physiological development.

In eidetic imagery, as in autoscopy, the factors of *sex* and of *intelligence* have no etiological significance, though certain psychological traits may be regarded as precipitating in both conditions. Thus, Saltzman and Machover found that in every case of eidetic imagery "the particular constitutional endowment of the individual may play an important role in their development."

Self-Appearance.—There seems to be a complete phenomenological identity between a self-appearance and an autoscopic double. They both are seen in the perceptual visual space; both seem to possess three dimensions and appear to obey the common laws of the nature. For comparison Case 42 of Tyrrell is quoted: "In 1929 Archbishop Frederic (E. J. Lloyd) . . . arrived home feeling very tired, sat down, and fell into a deep sleep, from which . . . 'I was sharply aroused in about a quarter of an hour. . . . As I awoke, I saw an apparition, luminous, vaporous, wonderfully real of myself, looking interestedly and delightedly at myself. Some books on a table back of my ghost I could see and identify. After I and myself had looked at each other for the space of about five seconds, my ghostly self vanished.'" The precipitating factors, i. e., the tiredness of the narrator, the transparent texture of the specter, and the way in which the subject was "sharply aroused" from his sleep, are identical with those met in autoscopy. (For instance, in our Case E. something "forced" the patient to wake up on each occasion he saw his double.)

Clairvoyance.—In the "circumpolar area," clairvoyance, or "sending of the soul" is performed professionally by a "possessed" shaman in a self-induced (apparently hysterical) trance. It is usually done for one of two reasons: (*a*) The shaman may "send his soul" to bring back the missing soul of a member of his tribe (whose body in the meantime remains in a hysterical stupor), or (*b*) he may "send his soul to the moon, and then have it come back to report what people up there are doing. In other cases he sends his soul for news to New York or to Hudson Bay post" (Linton [51]). It seems to be quite obvious that this form of clairvoyance has only a pretending character, resembling the make-believe nature of the imaginary companions in children.

In our culture, the clairvoyance occurs either (*a*) spontaneously (as in Case 36 of Tyrrell) or (*b*) experimentally (as in Cases 37 and 38). According to (*a*), the subject "spontaneously" sees the image of another (usually emotionally significant) person; according to (*b*), he is induced by another to "see" the suggested person. (Here the relationship between these two persons reminds one closely of the relationship between a medium and his hypnotizer.) Like shamans, the persons experiencing these phenomena fall into a trance-like state of altered awareness.

Sleep Hallucinosis.—This term comprises a group of visual hallucinatory experiences, which possess certain common features: They are connected with sleep; they are very vivid, are oftener visual than auditory, and show a characteristic "insight" in waking life; that is, "the subject who experiences them usually realizes their hallucinatory nature" (Henderson and Gillespie [35]). "Though they seem real at the time, their true character is readily recognized during waking life" (Brain [12]). Some of these vivid hallucinatory experiences occur in the drowsy state when the patient is just falling asleep (i. e., hypnagogic images); the others during sleep, consequently either waking the dreamer from his sleep (e. g., nightmares) or causing a quasiconscious behavior on his part (e. g., night terrors). Only the hypnagogic hallucinations will be further elucidated.

Hypnagogic images show the following peculiarities: They "behave" independently of the subject's voluntary control; they are characterized by a remarkable vividness of picture, with an unusual "variety of brilliant hues which surpass those of ordinary

experience" (Ardis and McKellar); the "seen" objects may show a change of size (either macropsia or micropsia); they possess a characteristic "microscopic clearness of detail" (Leaning), which resembles the unusual richness of details in "apparitions" (Tyrrell).

Hypnagogic hallucinations have some features in common with certain other visual experiences. 1. Thus, polyopia, which occurs in hypnagogic imagery, was noted also in mescaline intoxication (Klüver,[44,45]) and its variation is encountered sometimes in organic brain lesions in the form of "reduplication of body parts"; a similar experience of having two heads, one inside the other, was described by our Patient G. 2. Shifting of attention or change of attitude in eidetic images may result in the change of their content (Braddock); also the face of the double of our autoscopic Patient G. would change its outlines and clearness of detail with the change in the patient's attention and concentration; likewise, in hypnagogic images a too "close scrutiny may disrupt the image" (Ardis and McKellar). 3. Faces are frequently seen hypnagogically, and, in fact, this imagery has sometimes been called the "faces in the dark phenomenon" (Ardis and McKellar); similarly, four of the autoscopic patients in this series used to see either only or mostly their own faces.

According to Brain,[18] hypnagogic hallucinations are met mostly in sufferers from narcolepsy. However, Leaning, McKellar,[60] and McKellar and Simpson[61] believe that hypnagogic experiences are commoner than is generally assumed. "Visual hypnagogic images are experienced more often with closed than with opened eyes, they are more often coloured than not, and their subject matter is almost infinitely varied" (Ardis and McKellar[5]). In many respects they resemble the imagery of dreams, the eidetic phenomena, the visual experiences in mescaline intoxication (Maclay and Guttmann; Mayer-Gross), and the visual hallucinations in some psychiatric disorders.

Visual Hallucinations in Temporal-Lobe Lesions and Epilepsy.—The highly organized and elaborated visual hallucinations of the human form met in some organic cerely but also etiologically closely related to bral lesions are not only phenomenological-autoscopic experiences (patients of Dewhurst, Dewhurst and Pearson,[23] and Conrad[17]). They are believed to be mostly associated with temporal-lobe lesions. This was true in the cases of Pick and the following cases of Horrax (three of which were of a cyst and two of a glioma in the temporal lobe).

Case 3: "H. L., during one night constantly saw a woman friend in the room. . . . The figure stayed in the room all night, and moved about but did not talk. It was always on the patient's left side. . . . When the patient turned her head to follow the figure, it would also go to the left and disappear."

Similarly, our autoscopic Case A. "would lose sight" of her double "as soon as she turned her head sideward, or up or down."

Case 5 of Horrax saw ". . . processions of queer figures marching on the ceiling"; Case 6 complained: "I see figures approaching me from the left side. They are never very distinct, but sometimes seem like little people, a little old woman, etc." (Here is resemblance to our Patient C., who also saw "little people," although in a synesthetic way.) Horrax's Case 7 said she saw "little people, and they are yellow." She occasionally saw a red colt and "a dog standing out in the field. He had pointed ears and brown spots." (The red and brown colors of this patient are identical with the colors attributed by our Patient E. to the garment of his double.) Patient 8 of Horrax, a school-boy aged 16, repeatedly saw a panoramic scene of men playing cards. The game would invariably end in a row. His complex visual hallucination was a visual aura of his epileptic seizures. This case seems to be a transition between known organic brain lesions (the boy had a glioma in his left temporal lobe) and temporal-lobe epilepsy, where a panoramic scene may constitute either a visual aura or an epileptic sensory fit itself.

There are many similarities between autoscopy and an uncinate fit. For instance, the feeling of unreality, so marked in our Cases A., B., and F., is often met in uncinate fits, characterized thus by Horrax: "During the few moments of 'unreality' or 'dreamy state' there appear . . . the

figures or sometimes the shadows of people. . . . These figures sometimes seem grotesque, sometimes fairly natural. Often they are diminutive [as in our nonepileptic Case C.], or more rarely, enlarged. In some cases the hallucination is stationary, in others it may seem to be coming toward [as in our Patient B.] or going away from the patient [as in our Case F.]. Also, in hypnagogic experiences and in dreams the "seen" images may change their size, and the apparent movement of the hallucinated objects met in uncinate fits occurs also in sleep hallucinosis (Brain's summary [12] on his patient, a young commercial traveler). The further characteristic feature of an uncinate fit is the déjà vu phenomenon and the experience of "panoramic memory." Sometimes "there is added forced thinking about a meaningless word or phrase" (Mayer-Gross et al.), as in Case F. The seizure is often concluded by a period of automatic behavior (as in Cases B. and F.). A similar account of visual phenomena connected with temporal-lobe lesion and epilepsy is given by Martin and Elkington.[56]

The Phantom Limb.—"A phantom limb is the term applied to the illusion of the existence of a non-existent limb or segment of a limb" (Wilson [101]). This phenomenon is not necessarily confined to an anatomical "limb." It may occur after amputation of any protruding part of the body; e. g., Riddoch [78] reported phantoms of the nose, of the glans of the penis, and of a nipple. A painful phantom of an extracted tooth is also common.

The phantom limb seems to be a universal phenomenon if the amputation takes place after the age of 3 to 5 years, i. e., after the body image has been developed and established. Thus, Randall [76] found, in his study of 100 amputee soldiers, that "95% of these patients had phantom sensations of some type." Yet the awareness of the phantom limb and the intensity of the syndrome vary in different subjects, depending greatly on their individual attitude toward the loss of their limb and on their previous adjustment.

Wilson distinguishes painless and painful phantoms: "The painless phantom soon becomes less obtrusive, and gradually shortens, to disappear into the stump. Painful phantoms may persist indefinitely and cause much distress." According to Kolb,[46] the pain in the phantom limb may return, after its initial disappearance, on such occasions as an intercurrent illness or the fitting of a prosthesis. Wilson found that "a phantom limb or part of a limb may be experienced as the aura of a sensory Jacksonian epileptic attack," and his personal case, in which the patient "suffered from epileptic attacks, which began with a sensory aura experienced in a pre-existing phantom" of his amputated left hand, bears an obvious resemblance to our Patient B.

The position in space of the phantom limb, like the position of an autoscopic double, varies a great deal, although it seems to be more anatomically predetermined. Some writers believe that it "is supposed to assume that posture that was last remembered by the person before the amputation" (Hoffmann [36]); others, e. g., Henderson and Gillespie,[35] think that in all cases the posture resembles that assumed by a hemiplegic extremity.

There are certain similarities between a phantom limb and an autoscopic double. For example, "not infrequently a phantom can pass through such solid objects as walls, beds, or the patient's own body" (Hoffmann). Likewise, the respective doubles of our autoscopic cases B. and F. could pass through a closed door. Pisetsky's case of "a 55-year-old male . . . with very painful phantom legs" resembles Patient C., who, however, instead of phantomizing and projecting his amputated penis, projected into the visual space his whole body, thus exemplifying Fenichel's [26] equation: "girl=phallus" (i. e., body=phallus). Also, the psychodynamics in the two cases are identical: a narcissistic in-

ability to accept the loss of some important body part. There is one more similarity: In both cases ECT brought about the disappearance not only of depression but also of the autoscopic double (in C.), or of a partial autoscopic double, i. e., of phantom limbs (in Pisetsky's patient).

As in autoscopy, there are two main theories explaining the etiology of the phantom limb: 1. The *organic theory* assumes that the anoxia of the nerve fiber in the scar tissue of the stump leads to a painful stimulation, projected then by the cortex into the nonexisting limb. This theory finds its corroboration in the fact that "a phantom limb is abolished by a lesion of the area of the opposite parietal cortex concerned with representation of the body-image" (Brain; Wilson; de Gutierrez-Mahoney.[32] A more peripheral surgical intervention, e. g., a spinothalamic chordotomy, may relieve the pain but does not influence the phantom limb (Falconer and Lindsay[25]). 2. According to the *psychological theory*, "the phantom limb represents a narcissistic inability to renounce the integrity of the body or acknowledge the symbolic castration and thereby accept a relatively inferior position" (Schilder[84]). Hoffmann sees in the phantom limb "a wishfulfilling hallucination serving the function as . . . denial of the loss of the parts and the possible painful emotion associated with this loss."

Delusional Reduplication of Parts of Body.—Apart from the proper "reduplication of parts of the body," the following phenomena may be included in this group: (1) illusions of the existence of another member; (2) illusions concerning the position of the limbs in space, and (3) illusional movements of phantom limbs and hemiplegic extremities. (The bibliography on these conditions may be found in the paper of Weinstein et al.[100]).

These phenomena occur in patients with organic brain lesions, most frequently those leading to a left-sided hemiplegia. Some examples follow: (*a*) Bechterew (cited by Weinstein) described under the name of "pseudopolymyelia" the case of a male patient with left hemiplegia, who claimed to have two left hands, three heads, and six feet. (*b*) A patient of Ehrenwald,[24] also with a left hemiplegia, had "a nestful of hands" in her bed; she later reduced their number to only two left hands: an "old," which she called a "bad one," and a "new," a "good one." (*c*) Riddoch[78] described a female patient with right parietal atrophy whose sensory Jacksonian attacks would begin with a feeling that she had two sets of toes on her left foot. Similar cases were reported by other authors (Golant-Ratner[31]).

There are two schools of thought explaining the etiology of this phenomenon: 1. The *organic theory* regards it, as well as anosognosia, as the result of an organic lesion destroying this particular area in the parietal lobe, where the image of that part of the body is represented. 2. The *psychodynamic theory* assumes that such lesion "initiates a reorganization of brain function, in which any member that the patient conceives of as damaged may be reduplicated" (Weinstein) and that "the patterns of reduplication may be used as symbolic mechanism to express . . . the denial of illness," as in cases of phantom limbs. This interpretation was well illustrated by Case 3 of Weinstein: This patient, who suffered from severe headache and drainage after removal of a brain cyst, claimed to possess two heads, one of which, his "main" head, was "doing well," had "no bad drainage," and experienced no pain.

Each of Weinstein's patients, "in addition to the reduplicatory delusions concerning the body, showed reduplication for place, time or person." For example, one of his female patients developed such a reduplication of person, after operation of her metastatic brain tumor: She claimed to have twin sons, "Bill and Willie," although in fact she had only one, Bill.

As in the cases of autoscopic experiences (which are supposed to occur also in "normal" subjects), "many of the symbolic mechanisms described occur in normal per-

sons. In myth, folklore, and art, reduplication of parts of the body are themes that express the feelings and motivations of a culture. In Oriental art, particularly, gods are portrayed with many heads to indicate great wisdom, and many arms to express great strength or many skills. In our patients are reminiscences of the hundred-armed giants Briareus and Gyes, the Hydra, in whom the loss of one head was replaced by two others, the four-legged centaurs of Mount Pelion, and Argus, the many-eyed watchman. What appear as bizarre curiosities are actually meaningful patterns of behavior related to other manifestations of symbolic expression" (Weinstein).

Etiology of Autoscopy

This question is far from being well and clearly understood. Although it is accepted that the autoscopic experience represents a hallucinatory projection of the body image into perceptual space, there exists difference of opinion as to the mechanism involved and the cause of the phenomenon. Of various etiological explanations and hypotheses, two deserve a more detailed discussion.

1. The *organic theory* assumes that the autoscopic hallucinations are caused by irritative lesions in the temporo-parieto-occipital areas. This school of thought has many adherents (Nouët [65]; Menninger-Lerchenthal [62]; Sollier; Hécaen and Ajuriaguerra [33]; Pearson and Dewhurst [67]) and finds corroboration in experimental work (e. g., Bollea [9]; Lyle [53]), as well as in clinical data. There is, however, among representatives of this theory disagreement as to the localizing value of the complexity of visual hallucinations: (*a*) The views of one group of writers (e. g., Lhermitte, Rea [77]) were thus expounded by Wilson [101]: "I associate the elaborate type of visual phenomena with temporal or temporo-occipital lesions, that is, lesions in association fields, and the cruder type with lesions of the receptive zones." Lyle confirmed the above experimentally [53]: "Hallucinations, especially of light and colour, or simple and stationary objects, may be induced by irritation of Area 18. More complex hallucinations are found with involvement of Area 19." (*b*) Other authors reject the idea that the complexity of visual hallucinations may serve as a topographical clue. For instance, Morton Prince stated [75]: "I do not think it is possible . . . that irritation of any particular focal area can produce such a complicated psychologic phenomenon as hallucination. . . . The mechanism is to be sought in either release of inhibition, permitting denervated mental symptoms to function autonomously and automatically, or in irritative impulses sent to distant regions and instigating similar complex mental processes." The findings of Sanford and Bair [82] and of Cairns [15] seem to substantiate Prince's views. Weinberger and Grant also declared [99]: "The categoric opinions that distinctive types of hallucinations are peculiar to either the temporal or the occipital lobe become highly doubtful," as the hallucinations require for their occurence "the integration of the entire brain." Yet the controversy continues. Walsh states [98]: "I am unwilling to accept the conclusions of Weinberger and Grant in toto."

2. The *psychological theory* stresses the role of psychological and physiological factors: Johnson [42] regards the complex visual hallucinations as "projections of previously stored memory pictures"; Allen,[1] "as a special kind of visual memories, which are projected into space as positive images with the original details and colours." Wagener expresses a similar view [97]: "As a result of experience, visual perceptions are projected as if they came from the outside world, so that even the blind 'see' the hallucinations"; e. g., almost all patients with hemianopsia "see" their hallucinations in the blind field of vision. Rea [77] explains visual hallucinations occurring in the blind field (in cases of hemianopsia) as being due to irritation of visual memory centers; (cf. Fuchs [27]). Brain explains on similar lines the narcoleptic and hypnagogic hallucinations regarding them as psychologically in-

termediate between normal dreaming and hallucinosis. Recently, Todd and Dewhurst[93] offered an etiological explanation of autoscopy in terms of a combination of psychological (e. g., narcissism, archetypic thinking), physiological (supernormal power of visualization), and organic factors (such as disturbance of the function of the somatognostic areas).

I should like to present my own etiological hypothesis. I suggest that the autoscopic phenomena should be divided into two main types: symptomatic and idiopathic autoscopy.

(*a*) "Symptomatic Autoscopy"

This consists of two groups: To the first, or "organic, group" belong all cases of autoscopy associated with a known organic brain lesion. It seems probable that in "visualizers" with a narcissistic preoccupation any organically precipitated visual hallucination might tend to take the shape of an autoscopic "double." Yet even in entirely organic cases a certain degree of subconscious compensatory or wish-fulfilling mechanism is usually involved. This applies even more to the second group, which is mainly composed of cases of *temporal-lobe epilepsy* with the uncinate type of seizure (Patients B. and F.) and of cases of *migraine*, with a very strange and bizarre behavior of the double (Lippman). The autoscopic hallucinations here are brought about by irritation of the cortex (e. g., by a transient angiospasm with short-lived and reversible metabolic disturbances), and not by a permanent organic lesion. Thus, this type might be called a pathophysiological group, in contrast to the first, truly organic, one, and it might be regarded as a transition from the symptomatic type, with a known underlying pathology, to a "functional" type, with an, as yet, unknown pathology. The last may be called the "idiopathic" type.

(*b*) "Idiopathic Autoscopy"

There are a good many reasons to assume that with the further development of our diagnostic techniques and a further refinement of our, still rather crude, methods of clinical examination, fewer and fewer cases of autoscopy will be ultimately included in this group in the future. Yet there will probably always remain a certain number of cases in which no organic, endocrinologic, or physiopathological basis of the condition would be discovered, and in which it would be justified to assume a "psychogenic" causation (in the meaning of some psychodynamic mechanism, of a compensatory kind, or of a self-defensive character, or, most probably, of a vicarious wish-fulfilling nature).

Some illustrations of this "idiopathic" form of autoscopy, are selected from the material under review: Case C. is a model of such an entirely psychogenic, presumably compensatory, and wish-fulfilling mechanism (denial of illness or of loss of an important body part). This rather simple man, who always liked music and once wanted to become a conductor, derived an undeniable pleasure from seeing his "other self" (in his subconscious identification—himself) conducting an orchestra. It was for him the very fulfilment of his long-cherished secret dreams, and also some (at least esthetic) compensation for his complete loss of the possibility of a normal genital sexual satisfaction. A similar mechanism (wish-fulfilling phantasies of omnipotence) was possibly at play in the real conductor, described by Bonnier,[10] who, while conducting, "saw" himself as a giant looking downward upon his orchestra. There seems to be also no doubt as to the crude compensatory mechanism involved in the autoscopic experiences of Case D. His double supplied him with an easy outlet for his aggressive and sadistic impulses, helped him to bolster his self-esteem, provided him with a submissive "quasi-imaginary" companion, who had to take plenty of punishment from his severe "master."

Antithetical Clinical Syndromes

It may be of interest just to mention some comparatively rare clinical syndromes, which *phenomenologically* present an antithesis of

autoscopy. While in the latter there is a "reduplication," a "duality," or a "schism" of the body image, with its projection into perceptual visual space (the "hyper-" and "paraschematia," in Critchley's [20] terminology); in the conditions I shall very briefly review, there is a failure of perception (or of recognition) of the patient's own body parts which became paralyzed (Critchley's "a-" or "hypo-schematia"). *Psychodynamically*, these conditions are identical with the hyper-, or paraschematic group; i. e., they represent a denial of illness, or loss of function in an important body part. They resemble the first stage of a "phantom limb," or of a reduplication of (diseased) body parts: The patient denies (or fails to admit) the loss of function of a paralyzed limb, but does not reduplicate it or create a phantom limb. Some patients, however, go further and reach the second stage in their denial of disability, the stage of producing a "phantom," but only symbolically (and half-heartedly) in form of their overcompensatory and wish-fulfilling behavior; e. g., they "not only deny their blindness but behave as though they can see and, when tested, confabulate, describing purely imaginary visual experiences" (Wilson). (We have a patient now in the ward, a man with spastic paraplegia, who boastfully tells that he just came back from a long walk, etc.).

A few examples of these disturbances of body image follow. "Autotopagnosia" (Pick), or "somatotopagnosia" (Gerstmann [29]), is the name for the loss of perception of parts of the body. "Anosognosia" is Babinski's [6] term for the unawareness of hemiplegic extremities. Similar cases were reported by Stengel and Steele.[92] Anton [3,4] described patients with "anosognosia" for their blindness or deafness or aphasia. The denial of hearing difficulties is quite a frequent and well-known occurrence. Schilder and Stengel [85,86] described 10 cases of "asymbolia for pain," a condition in which the subjects perceived the sensation of pain but had lost the appreciation for its unpleasant character. Hemphill [34] reported a case of "misinterpretation of mirror image of self," where the patient would not recognize herself in a mirror and persistently mistook her own reflection for the face of her deceased sister. A similar condition, but not related to one's own body, has been called "loss of visual imagery for objects" (Wilson). For instance, Charcot (cited by Wilson) described a patient who lost visual memory for forms and colors and could not visualize his wife and his children. Wilson himself had two patients who "lost all visual imagery in dreaming" and could not "draw objects from memory," though they did not suffer from a visual object agnosia. "Gerstmann's syndrome" [30] includes finger agnosia, agraphia, acalculia, and right- and left-sided confusion, and is caused by lesions of the respective parietal areas.

Autoscopic Phenomena in "Normal" Persons

Many authors believe that seeing one's double occurs also in completely "normal" subjects. For example, Dewhurst expresses the view that "an occasional hallucination is by no means a rarity in the sane." Similarly, Smythies [89,90] says that "visual hallucinations, in the form of hypnagogic and eidetic imagery, occur so frequently in normal people, that they cannot reasonably be considered as abnormal, or pathological in themselves. . . . The formation of hallucinations is a normal activity of the mind." Nielsen [64] goes even further: "Inasmuch as hallucinations are merely activity in the cerebral cortical areas of recall . . . they do not of necessity have any psychotic significance even when accompanied by delusions of their reality." Also, Conrad appears to believe that "normal" subjects may experience autoscopic hallucinations, as it may be assumed from his division of autoscopic phenomena into three groups, whereby to his . . . "first group belong all these experiences of psychically normal, who report to have met unusual phenomenon of seeing their own double."

Conclusions

1. The "double" appears usually suddenly and without warning.

2. In epileptic and migrainous patients an autoscopic experience may occur before, instead of, or after, an attack.

3. Most frequently the subject "sees" only the face, or the face and the bust of his double; less frequently, the whole figure, usually life-sized.

4. The specter is seen clearly and with details.

5. With a few exceptions, the double has generally no color.

6. Its texture is most frequently transparent.

7. The double usually imitates all movements, in particular, the facial expression, of its "original."

8. The subject of autoscopy commonly perceives his double with more than one sense. In addition to visual sensation, he may experience auditory, kinesthetic, emotional, and intellectual perception.

9. The most frequent emotional reaction to seeing one's double is sadness, often amazement or bewilderment, sometimes satisfaction, and in schizophrenic subjects indifference.

10. The subjective sensory feeling of coldness and weariness seems to be the most frequent one.

11. There is a peculiar detached "insight" into the unreality of the experience.

12. The most frequent localization of the double is the visual space straight in front of the patient, about a yard away, although in some migrainous subjects the localization may be most phantastic, defying all laws of gravitation.

13. The whole experience lasts usually a few seconds at a time.

14. The frequency of occurrence fluctuates from once in a lifetime to a continuous presence of the double, the patient being all the time on the fringe of full awareness of it.

15. The great majority of phantoms appear at dusk, a few only in the daytime.

16. Sex does not seem to be of any etiological significance in autoscopy.

17. Neither intelligence nor education is of any relevance.

18. Age itself does not play any important part in autoscopy.

19. There seems to be no morbid heredity in subjects of autoscopy.

20. There is no causal relationship between autoscopy and psychosis.

21. There seems to be more than a mere chance affinity between autoscopy and epilepsy and migraine, but its character is at present unknown.

22. No treatment of autoscopy is known, though a symptomatic therapy of some coexisting disorder (e. g., of depression) might prove to be beneficial to autoscopy as well.

23. There exists a phenomenological and psychodynamic relationship between autoscopy and such parahallucinatory phenomena as imaginary companions, eidetic images, self-appearances, clairvoyance, hypnagogic imagery, and some "anatomically incomplete" body-image disturbances, such as phantom limb and the group of delusional reduplication of parts of the body.

24. There are two main etiological theories: the organic, which regards autoscopy as the result of some irritating process in temporoparietal lobes, and the psychological, which sees in autoscopy the projection of "memory pictures." A personal hypothesis recognizes symptomatic autoscopy, with a known organic causation, and idiopathic autoscopy, interpreted in terms of a compensatory or a wish-fulfilling mechanism.

25. Many authors believe that some "normal" subjects, in particular "visualizers" with narcissistic character traits, may "see" their "double" occasionally, especially in conditions of mental stress.

Summary

The history and the definition of autoscopy are given. Seven personally studied cases of autoscopy are briefly described. A comprehensive clinical picture of an auto-

scopic "double" is sketched. Some related phenomena, and their similarity to autoscopy, are discussed and evaluated. The etiological theories are elucidated, and a personal hypothesis is advanced. The occurrence of autoscopy in "normal" subjects is considered.

2, The Cottage, Barrow Hospital.

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Cerebrospinal Fluid Neuraminic Acid Deficiency in Schizophrenia

SAMUEL BOGOCH, M.D., Ph.D., Boston

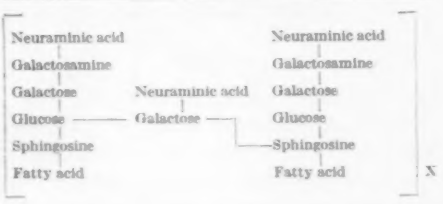
With the thought that metabolic disturbances nuclear to the schizophrenic process might best be studied in the central nervous system itself, the attention of this laboratory has been directed to certain little-known chemical constituents of the brain and cerebrospinal fluid.[1-7] The presence of neuraminic acid as a normal constituent of the macromolecular brain gangliosides suggested that its study in cerebrospinal fluid might afford a ready and repeatable source of pertinent information.

The mean neuraminic acid content of cerebrospinal fluid in schizophrenic patients is here shown to be considerably below that of nonschizophrenic adults and comparable only to values found in some children under 7 years of age.[7] The present report describes the preparation of neuraminic acid standard from bovine brain ganglioside, the detailed procedure for the estimation of neuraminic acid in cerebrospinal fluid, and the values found in what is now a total of 195 subjects. A later communication will describe micromethods which have been developed for the determination of the distribution of neuraminic acid and other carbohydrate constituents among various chemical components of the cerebrospinal fluid of individual patients.

Methods

Preparation of Neuraminic Acid Standard.—The preparation of ash-free brain ganglioside, together with hydrolytic studies which have led to the formation of the structure of its repeating unit as shown in Table I, is described in detail elsewhere.[8] Neuraminic acid is prepared from ash-free brain ganglioside as follows[8,5,6]: A 2% aqueous solution of ash-free brain ganglioside is heated at 100 C for exactly 20 minutes. The solution is cooled and transferred quantitatively to a prewashed cellophane bag and dialyzed against twice its volume of distilled water at 4 C. The diffusate is collected after 12 hours and replaced with fresh distilled water, and this procedure is repeated until no further diffusible material is obtained (dry weight of final diffusate less than 1 mg.). The combined diffusates are lyophilized and represent "neuraminic acid fraction 1." This material is further purified by partition with cold methanol, the amorphous material being solubilized, while the crystalline neuraminic acid remains insoluble in cold methanol. The crystalline material is twice repartitioned. The final product contains nitrogen 4.5%, a reducing

TABLE 1.—*Proposed Structure of Repeating Unit of Brain Ganglioside*



	Constituent % of Brain Ganglioside	
	Calculated on Basis of Above Formulation	Found
Nitrogen	2.96	2.9
Neuraminic acid	30.5	30.3
Hexose	24.4	24.0
Galactosamine	10.8	10.0

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Neurochemical Research Laboratory, Massachusetts Mental Health Center, and Department of Psychiatry, Harvard Medical School.

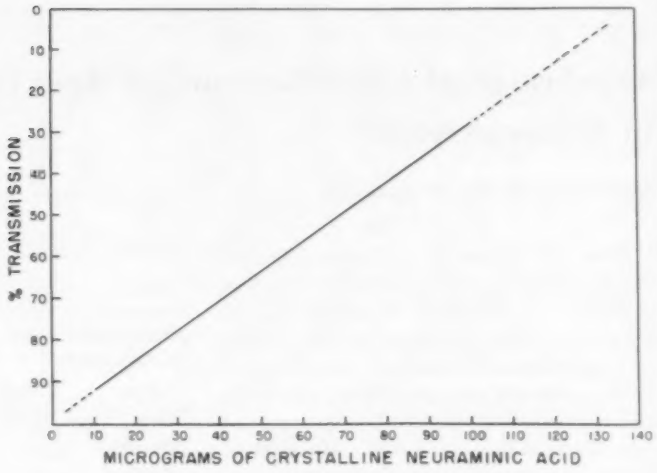

Fig. 1.—Standard curve for determination of neuraminic acid in cerebrospinal fluid.

sugar of 61.4% (as galactose), no galactosamine, and no galactose, and possesses no absorption peak at 2700 A. units. aqueous solutions of this material, 5μg. to 100μg. per cubic centimeter, are used to obtain the standard curve by the method described below. The curve which has been employed is shown in Figure 1. The standard curve is verified at biweekly intervals, and with any new stock reagents, including amyl alcohol. Furthermore, it has been found that an aqueous solution of crystalline neuraminic acid changes on standing to a substance which possesses an absorption peak at 2700 A., and which gives a diminished color reaction with Bial's reagent.[8] It is therefore of critical importance that crystalline neuraminic acid, which has been kept dry in vacuo and in the dark, be employed in the initial preparation, as well as in later verifications of the standard curve.

Determination of Neuraminic Acid in Cerebrospinal Fluid.—Source of Specimens: Cerebrospinal fluid obtained in routine diagnostic and anesthetic lumbar punctures from four general and two mental hospitals were examined without knowledge of the diagnosis. Hexose, protein, and neuraminic acid determinations were done on samples which contained less than 3 red blood cells per cubic millimeter. Bloody samples were not used because of the contribution of serum neuraminic acid.

Reagents:

1. Bial's reagent[10]

Concentrated HCl	40.7 cc.
Orcinol	0.1 gm.
1% $FeCl_3$ (aqueous solution)	1.0 cc.
Dilute to 50 cc. with glass-distilled water	

Prepare fresh daily

2. Normal amyl alcohol, reagent grade (Mallinckrodt Chemical Works)

Procedure: One cubic centimeter samples of fresh cerebrospinal fluid (determined no longer than four hours after lumbar puncture and refrigerated at 4 C during this time) are placed in 12 cc. centrifuge tubes. One cubic centimeter of Bial's reagent is added; the contents are mixed, and the tubes are capped with aluminum foil and heated in a vigorously boiling steam bath for exactly 15 minutes. The tubes are removed and cooled in ice-cold water. Amyl alcohol, 5 cc., is added to each tube. The two phases are thoroughly mixed with a stirring rod for exactly 30 seconds and the tubes centrifuged for two minutes. Two reagent blank tubes are run with each determination and contain 1 cc. of glass-distilled water and 1 cc. of Bial's reagent. The reagent blanks are treated exactly like the samples. After centrifugation, two clear phases are present. The upper phase is carefully decanted into a small colorimetric tube (3 cc.), with care that none of the lower phase is transferred. The reagent blank tubes are read against distilled water on a Coleman Jr. spectrophotometer at 570 mμ in terms of percentage transmission. The reagent blank is then set to 100% transmission and the cerebrospinal fluid samples read against the reagent blank. Micrograms of neuraminic acid are read from the standard curve above.

Precautions: The above described determination requires scrupulous microchemical technique, chemically clean (acid-washed) glassware, including the containers in which the cerebrospinal fluid is first collected, and calibrated volumetric pipettes.

In addition, the following aspects of the determination have been found to be critical:

1. The cerebrospinal fluid must be fresh. While some of the samples show no change in total neuraminic acid content on repeated daily determinations, the value in some changes markedly on standing over a few days. These changes, which may be related to the changes in crystalline neuraminic acid on standing described above, are under investigation. From the point of view of obtaining comparable values, however, only fresh cerebrospinal fluid is reliable, and the arbitrary limit of four hours after puncture is employed.

2. The tubes must be carefully covered and the steam bath kept vigorously boiling (100 C), since the difference of a few degrees in temperature makes a considerable difference in color development. The timing must be exact.

3. The amyl alcohol used has been from one company (Mallinckrodt, No. 2996). The mixing of the phases during extraction of the color must be timed exactly, and none of the resultant lower phase must be transferred to the colorimetric tube.

With these precautions the determination is quite accurate, duplicates checking within ±1%. Because of the narrow range of values, duplicates which do not check within ±1% are not considered valid.

Determination of Hexose: Hexose was determined by the method of Sørensen and Haugaard[8] and expressed in terms of milligrams of glucose per cent.

TABLE 2.—*Neuraminic Acid Concentrations in Cerebrospinal Fluid*

	Age, Yr.	No. of Patients	CSF Neuraminic Acid, μg/Cc. Median	Mean
Schizophrenic patients	20–65	29	36.0	35.5
General hospital children	0.2–6	72	43.0	42.3
General hospital children	7–15	20	45.5	47.0
Nonschizophrenic mental hospital adults	16–61	19	49.0	51.6
General hospital adults	20–86	46	55.0	58.3

Determination of Protein: Protein was determined by the sulfosalicylic-acid method.[9]

Results

The results obtained are summarized in Table 2. The mean concentration of cerebrospinal fluid neuraminic acid in adult schizophrenic patients is lower than that of nonschizophrenic subjects, and comparable only to values found in some children under the age of 7 years. None of the patients in the category "nonschizophrenic mental hospital adults" had any known organic disorder whatsoever. Twenty-five of the patients in the category "general hospital adults" had no disorder of the nervous system, the spinal fluid having been obtained on the occasion of a lumbar

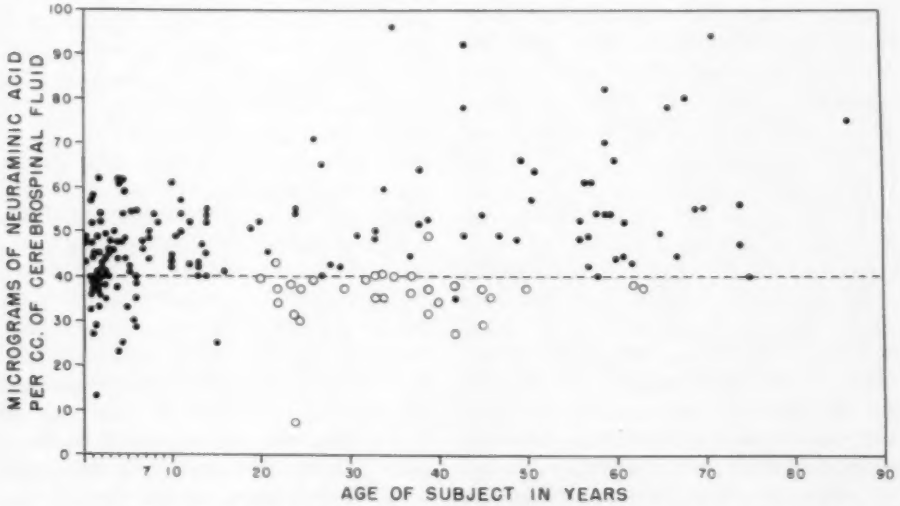

Fig. 2.—Cerebrospinal fluid neuraminic acid concentration as a function of age. Solid circles indicate nonschizophrenic subjects; clear circles, schizophrenic subjects. The broken line indicates only the 40 μg/cc. level.

puncture prior to spinal anesthesia for minor surgical procedures (hemorrhoidectomy, hernia repair, etc.).

Each determination is plotted in Figure 2 as a function of the age of the patient. It may be seen that there is a tendency among the nonschizophrenic subjects for the concentration of neuraminic acid in cerebrospinal fluid to increase with age. There is clearly an individual difference, however, in the concentration achieved by individual subjects. Thus, about 40% of children under 7 years of age have values of 40μg. per cubic centimeter of cerebrospinal fluid and less, whereas the rest are already at more "adult" levels. However, with the exception of 5 out of 94 subjects, all nonschizophrenic subjects over the age of 7 years had neuraminic acid levels above 40μg. per cubic centimeter. On the other hand, with the exception of 2 out of 29 cases (6.9%), all patients with the clinical diagnosis of schizophrenia were found to have neuraminic acid levels at or below 40μg. per cubic centimeter.

On the consultation of the clinical records of the five supposedly nonschizophrenic subjects over 7 years of age, who were actually in general hospitals for somatic disturbances and who had neuraminic acid values below 40μg. per cubic centimeter, three were found to have schizophrenia-like disorders. Thus, one was a 23-year-old man with a psychosis diagnosed as "obsessive-compulsive," who had had three mental hospital admissions; the second was a 13-year-old girl whose condition was diagnosed in a general hospital as "conversion hysteria" because of three attacks of a negativistic, coma-like state; the third was a 40-year-old patient with a severe "psychoneurotic" illness with schizoid features, who had been under psychiatric care for many years. The remaining two were a 12-year-old boy and a 42-year-old woman, neither of whom had a history of mental disorder. The current "diagnostic error" for nonschizophrenic subjects past the age of 7 may, therefore, be considered to be 2 in 94 (2.1%). If the five nonschizophrenic subjects more than 7 years of age who had values of exactly 40.0μg. are included, this error becomes 7 in 94 (7.5%).

The mean content of cerebrospinal fluid neuraminic acid in nonschizophrenic mental hospital patients (including those with manic-depressive psychoses) is much above that of schizophrenic patients. It is also somewhat below that of general hospital adults (Table 2).

The total neuraminic acid was found to be independent of the total protein content of the cerebrospinal fluid, with the exception of subjects with protein values greater than 70 mg. %, in which case the neuraminic acid was usually, although not always, in the high range. The neuraminic acid values were also found to bear no constant relationship to the glucose values for cerebrospinal fluid.

Comment

The content of neuraminic acid of the the cerebrospinal fluid of schizophrenic patients has not been reported hitherto. The method here used for the determination of neuraminic acid is a modification of that employed by Klenk and Langerbeins.[10] Böhm et al.,[11,12] Roboz et al.,[13,14] and Uzman and Rumley[15] have determined some neuraminic-acid-containing fractions in blood and cerebrospinal fluid. It may be noted that none of the last three authors reported the preparation of his own neuraminic acid standard for these determinations, and the animal source, as well as the purity of neuraminic acid standard employed, may not have been identical. Also, several differences in the methods exist. Studies in this laboratory on the distribution of neuraminic acid between macro- and micromolecular species in cerebrospinal fluid suggest that the values for trichloroacetic acid or alcohol-precipitable neuraminic acid, which the above authors reported, correspond only to the protein-bound neuraminic acid, which, in turn, accounts for

only 18% to 25% of the total neuraminic acid in cerebrospinal fluid,[16] thus explaining possibly the low values which they obtained.

The determination of cerebrospinal fluid neuraminic acid must be performed on a larger number of cases before any definite conclusion can be drawn regarding its diagnostic value. To date, low values in adults correlate well with the clinical use of the term schizophrenia, whether it be an acute first admission or a chronic process of over 10 years' duration. The few cases in which it does not so correlate may represent the inherent diagnostic error of the determination. It may also support the idea that the clinical use of the term "schizophrenia" may embrace more than one type of disordered process. If the latter is so, it is still somewhat surprising that, at least in terms of the single parameter of total neuraminic acid content of cerebrospinal fluid, there is agreement in 93% of the cases so classified. It is possible that this agreement would support the concept of a unitary disease process rather than that of a multiplicity of similar symptom formations operating in most patients with an illness diagnosed as schizophrenic.

While there have been numerous attempts in the past to demonstrate some metabolic disturbance in schizophrenia through the study of blood and urine, there has been no unequivocal demonstration of a chemical disorder in the central nervous system proper. Thus, the above findings of a decreased content of neuraminic acid in the cerebrospinal fluid of schizophrenic patients would appear to indicate an important new area for further investigation. Because of the present lack of knowledge of the intermediary metabolism of neuraminic acid, it is not yet possible to interpret with any certainty the meaning of a lowered value of neuraminic acid in the cerebrospinal fluid.

The tendency for the concentration of neuraminic acid to increase with age suggests a relationship to maturation. Low values in adult schizophrenic patients, comparable only to those found in some children under the age of 7 years, may indicate a form of chemical immaturity of the nervous system. While, as yet, no other chemical changes in the nervous system itself have been reported for this age, it may be noted that other metabolic and psychological changes have been independently demonstrated to occur at this period of life. Thus, between the sixth and the eighth year the excretion of 17-ketosteroids in both male and female subjects shows a marked upward trend toward adult levels,[17] and the excretion of estrogens increases.[18] From a psychoanalytic point of view, the latency period has just begun. The work of Pollack and Goldfarb[19] is also of interest in this regard. These authors have shown that the acquisition of particular perceptual skills, as demonstrated by the "face-hand" test, occurs at about this age, and that schizophrenic children over 7 years of age show a disability characteristic of children under 7.

Neuraminic acid is a normal constituent of the gray matter of brain, where it occurs in combination with carbohydrate and lipid substances in the form of the macromolecular brain ganglioside (Table 1). While the function of neuraminic acid in the nervous system is not as yet clearly defined, there are a few clues of interest. For example, brain ganglioside has been shown by me to be an active inhibitor of the viral hemagglutination reaction of influenza PR8 virus, and the constituent neuraminic acid of brain ganglioside has been shown to be essential for the inhibitory reaction.[6] The structure of brain ganglioside, as formulated above, fits this substance admirably to function at cell-membrane surfaces. The di-soluble properties of brain ganglioside, the arrangement of its constituents, and its acidic functions would suggest that it might be involved in the functions of the blood-brain barrier.[7]

The presence of neuraminic acid in the circulating component of the central nervous system, i. e., cerebrospinal fluid, its association with the proteins of this fluid, and the demonstration above of its variation in concentration suggest that there may be, in

addition to the classical concept of a fixed blood-brain barrier function, a circulating component associated with antibody functions. The term barrier-antibody system is thus proposed to denote both fixed and circulating barrier components, whose functions are defense, and the maintenance of a selective internal environment for the brain. The term "barrier" as used here represents not a static function, but, rather, the net effect of an active exchange of substances across a membrane.

The present demonstration of the tendency for the concentration of cerebrospinal fluid neuraminic acid to increase with age in humans suggests that this substance may be involved in maturation processes in the nervous system. The failure of chemical maturation exhibited by the schizophrenic patient would correlate meaningfully with clinical evidence demonstrating a failure in psychological maturation. Thus, if the function of the barrier-antibody system is the maintenance of a selective environment for the brain, then the failure of this system could account for the disorganization which is manifest in the psychotic state. Since the classical blood-brain barrier is lowered under the influence of various stresses and inflammations, and with the increased secretion of adrenocorticoids,[20] the psychotic episodes which may occur under these conditions may be directly related to the lowering of barrier functions.

Viewed in this light, there is no need to seek specific toxins as "causal agents" in schizophrenic psychoses, but, rather, it is possible that normal metabolites, which are usually prevented from coming into prolonged contact with the brain, may, when they do so, so interfere with the normal metabolic environment that disorganization of function ensues. It is further possible to conceive of anxiety, with its physiological accompaniments, as the critical agent in the development of the psychotic state by means of its effect upon the barrier-antibody system. The possession of an inadequately developed barrier-antibody system would represent a specific vulnerability to psychosis.

While alternative interpretations with reference to these findings are possible, the above hypothesis has the following advantages:

1. It derives from data on the chemical constituents of the central nervous system proper, rather than from data obtained on substances like blood and urine, which carry the pooled metabolites of all the body organs.

2. It is consistent with our current understanding of psychological defects in maturation and their relationship to psychiatric disorders.

3. Most important, it leads to the development of working hypotheses which are readily susceptible to experimental validation or negation.

In addition to experiments designed to test barrier functions in patients, it will be of some interest to determine the effect of the administration of neuraminic acid itself and of neuraminic-acid-containing substances to psychotic patients. These experiments are in progress.

Summary and Conclusions

1. The mean neuraminic acid content of cerebrospinal fluid in schizophrenic patients is shown to be considerably below that of nonschizophrenic adults, and comparable only to values found in some children under 7 years of age.

2. The method employed for the preparation of crystalline neuraminic acid from purified bovine brain ganglioside for use as standard is detailed.

3. The method employed for determination of neuraminic acid in cerebrospinal fluid, together with the precautions to be observed, is described.

4. The concept of a barrier-antibody system and its possible relationship to the psychoses is presented. The susceptibility of this hypothesis to experimental validation or negation is stressed.

5. It is concluded that an important new area for further investigation has been indicated.

Dr. Harry C. Solomon made available the facilities of the Massachusetts Mental Health Center. Cerebrospinal fluid specimens were supplied by Dr. Karl Dussik, of the Metropolitan State Hospital; Dr. William H. Sweet, of Massachusetts General Hospital; Dr. Allen Crocker and Miss Winifred Campbell, of the Childrens' Medical Center; members of the surgical staff of the New England Deaconess Hospital, and members of the staff of the Massachusetts Mental Health Center.

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Massachusetts Mental Health Center, 72-76 Fenwood Rd. (15).

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The Digit Span Test and the Prediction of Cerebral Pathology

ALFRED B. HEILBRUN Jr., Iowa City

The use of the auditory-vocal digit span test in clinical examination procedures is based on the assumption that it usefully reflects the status of an important area of intellectual functioning. When defective performance on this immediate memory task is observed, the most frequent diagnostic inferences are those of anxiety-induced interference or of impairment associated with a cerebral disorder. This study concerns itself with the latter inference.

The findings of many studies would support the use of a digit span task for the diagnosis of brain damage (BD) in adult nonpsychotic patients.[1-3,6-14] Only one study in which the digit span test could be independently evaluated showed a failure to discriminate between BD Ss and non-BD Ss.[5]

Despite the rather convincing evidence that digit span performance permits some degree of prediction, a clinician wishing to utilize this test needs more specific information. None of the studies cited above has addressed itself to the problem of establishing cut-off points for maximal discrimination between BD and non-BD Ss and of determining the predictive validity associated with these cut-off points. The present study provides estimates of these statistics.

Procedure

The seven independent samples of digit span performance included in this study were collected from various institutions in the State of Iowa over the past five years. Participating institutions included the University Hospital and Veterans' Administration Hospital, Iowa City; the State University of Iowa, Iowa City; Veterans' Administration Hospital, Knoxville, and the Mental Health Institute, Independence. The samples may be classified in the following fashion:

1. Brain-damaged Ss. This sample includes nonpsychotic Ss with confirmed or suspected cerebral pathology obtained from neurological or neurosurgical services (N=171).

2. Schizophrenic Ss (Schiz.) (N=136).

3. Manic-depressive Ss (M-D). This group includes both depressed and manic types, since their performances did not differ significantly (N=22).

4. Psychoneurotic Ss (Ntc.) (N=136).

5. Physically ill normal Ss (PI). These were hospitalized Ss with no suspected cerebral pathology (N=131).

6. Ward attendants (HA). These Ss constituted the healthy, "average" intellect group (N=27).

7. College undergraduates (HS). These Ss made up the healthy, "superior" intellect group (N=233).

In order to reduce the decremental effects of aging upon digit span performance, no Ss over 50 years of age were utilized in the study. The samples were matched for age and education except for the one composed of college undergraduates. Data concerning the age and education variables are presented in Table 1.

The digit span task used in the present study was the standardized procedure, which constitutes identical subtests of the Wechsler-Bellevue I[15] and the Wechsler Adult Intelligence Scale. Raw scores, defined as the number of correctly repro-

TABLE 1.—*Age and Education Means and Standard Deviations for the Various Samples of Ss*

	BD	Schiz.	M-D	Ntc.	PI	HA	HS
Age							
Mean	34.8	34.9	35.4	32.7	33.8	33.5	21.0
S. D.	9.7	6.4	9.0	7.3	8.2	7.1	3.8
Education							
Mean	10.2	10.5	11.1	10.5	10.3	10.6	13.4
S. D.	3.2	3.1	2.3	2.3	2.6	2.2	1.5

State University of Iowa.

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TABLE 2.—*Percentage of Cases in Each Sample Which Would Be Classified as Brain-Damaged with Various Samples of Ss**

Cut-Off Point	BD	Schiz.	M-D	Nte.	PI	HA	HS
5	4	1	0	1	0	0	0
6	8	3	0	1	0	0	0
7	13	12	4	6	5	0	0
8	26	22	18	14	16	15	3
9	53	40	36	30	31	15	11
10	71	54	55	50	54	41	30
11	82	75	77	68	70	48	48
12	90	83	86	79	81	67	64
13	96	91	91	89	89	78	77
14	98	94	95	93	93	85	88
15	99	97	100	97	97	93	95
16	100	99	100	98	99	96	97

* A cutting score of 10, for example, would mean that all Ss with digit-span raw scores of 10 or less would be classified as BD.

duced digits forward plus the correct number backward, were used as the criterion variable.

Results

Table 2 presents the percentage of Ss in each sample classified as BD for the range of digit-span cutting scores. Although it is possible to obtain raw scores of 0, 2, 3, or 4 on this test, these scores were not considered, since only 6 of the total 856 Ss, or less than 1%, obtained such scores. The maximum possible raw score of 17 was also not considered, since utilizing this as a cutting score automatically classifies anyone tested as BD.

Using the percentage overlap data found in Table 2, cutting scores providing optimal discrimination for each BD and non-BD comparison were established. An estimate of predictive validity associated with each optimal cut-off point was computed by averaging the percentage of Ss correctly classified in the BD group and in the non-BD comparison group. These data are shown in Table 3.

Comment

By comparing the digit span performance of Ss with confirmed or suspected cerebral pathology with the performance of various psychiatric and nonpsychiatric control samples, optimal cutting scores for group discriminations were determined, as well as the percentage of correct classification associated with these cutting scores.

It seems reasonable to conclude from the results of this study that, despite the established sensitivity of the digit span test to cerebral pathology, the test still falls short of being a useful method of discriminating between BD and non-BD Ss when used as an independent measure. Even with optimal cutting scores, predictions based on this test lead to about 40% misclassifications when brain-damaged patients are compared with hospitalized physically ill, neurotic, or psychotic patients. When nonhospitalized normals comprise the comparison groups, discrimination is enhanced, as would be expected. However, the classification error of about 30% when BD's are compared with bright, young college Ss probably represents a near-maximum expectancy for this test as a discriminating device.

The question might be raised as to the effect upon digit-span discriminations of the age restriction of 50 years or less for the Ss in this investigation. If, for example, there were a *differential* decline in this type of immediate memory ability in the direction of poorer performance for older BD Ss, as compared with older non-BD Ss, the statistics in this study would tend to underestimate the discriminative effectiveness of the test in a wider age-range population. To test this possibility, the digit-span performance of 75 BD Ss over 50 years of age (mean age, 59.8 years) were compared with the performances of 27 comparable PI Ss (mean age, 55.5 years). The mean raw score for the older BD group was 8.43, as compared with 9.44 for the BD Ss in the study. This mean for the older PI group was 9.39, as compared with 10.65 for the PI Ss reported in the investigation. Since the older PI's demonstrated a mathemati-

TABLE 3.—*Optimal Cut-Off Points for Discrimination Between BD and Non-BD Groups and Estimates of Predictive Validity*

	Schiz.	M-D	Nte.	PI	HA	HS
BD	10	9	9	9	9	9
Percentage correct Classification	58.5	58.5	61.5	61.0	69.0	71.0

cally greater performance decrement than did the older BD's, it does not seem tenable to assume that the age restriction operated against the discriminative effectiveness of the test.

There are many possible hypotheses to account for the limited discriminative capacity of the digit span test. Difficulty in concentration associated with heightened anxiety or inadequate motivation, which would tend to depress performance levels in the non-BD groups, immediately suggests itself. Thought confusion, characteristic of a schizophrenic group, would have the same effect. Finally, the possible association between brain pathology and schizophrenia could be mentioned in this context. Such speculation seems less important, however, when it is recalled that the tests yielded only 71% correct classification when BD's were compared with a college group not characterized by any of these performance-depressing attributes.

It is interesting that, despite the differences in non-BD-group performances, particularly between hospitalized and nonhospitalized Ss, the optimal cutting scores for BD discrimination remained remarkably stable. A raw total of 9 constituted this score for all groups with the exception of schizophrenics.

It would be by no means mandatory that a clinician use the percentage overlap data in Table 1 in the same fashion as has been done in this study. The optimal cutting-score approach presupposes that equal importance is attached to false-positive (classifying non-BD's as BD) and false-negative (classifying BD's as non-BD) errors. In certain situations it might be deemed advantageous to decrease the risk of one type of error at the expense of increasing the risk of the other. For example, the clinician in a mental hospital might wish to minimize the possibility of failure to detect cerebral pathology in order to avoid assignment of such patients to electroshock treatment, which could exacerbate the condition. In such a case the cutting score would be increased.

If in the future the digit span test continues to be used for prediction of cerebral dysfunction, it appears legitimate to recommend that a standardized procedure, providing empirically determined cutting scores and probabilities of correct classification, be used. In this fashion the clinician, operating actuarially, can make the most of the limited capacity of the test and operate within established error limits.

This is not to say that psychologists should necessarily accept the limited effectiveness of the test without attempting to improve it. For example, Blackburn and Benton [4] have recently devised a new administration and scoring procedure intended to increase the reliability of the digit span test. With an augmented number of items, they were able to increase the test-retest reliability from approximately 0.70 to approximately 0.80. While greater reliability does not necessarily lead to increased validity, it is reasonable to suppose that it might well have this effect on the digit span test, which has a relatively low reliability in the form in which it is typically given.

Summary

This study assessed the effectiveness of a standardized digit span test in discriminating between Ss with known or suspected cerebral pathology and various groups of non-BD Ss. The performance of the BD sample was compared with that of hospitalized psychotic, neurotic, and physically ill Ss and normal hospital ward attendants and college students. Empirically derived cutting scores were determined for optimal discrimination between BD's and each type of non-BD group. The predictive validity of the digit span test for each of these cutting scores in terms of the percentage of correct classification was then computed.

The findings suggest the variable, but generally limited, effectiveness of the digit

span test as an independent predictor of cerebral pathology.

Dept. of Psychology, State University of Iowa.

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The Sedation Threshold

Its Concept and Use for Comparative Studies on Drug-Induced Phenomena

ALI A. KAWI, M.D., Dr. P.H., Med. Sc.D., Brooklyn

The concept of the sedation threshold, recently introduced into the medical literature, has received considerable attention as a tool of value in psychiatric and psychosomatic research. It acquired its significance from the findings that it correlated with two important and fundamental determinants in the psychological and psychoanalytic theory: the degree of anxiety and the degree of impairment of ego functions. It also acquired another value as a relatively constant level for the individual and a relatively enduring biological characteristic of him, as indicated by a high test-retest reliability in studies of the sedation thresholds for amobarbital (Amytal) sodium.[10]

A study has been undertaken to investigate the relationship between various manifestations that have been designated "anxiety" and the amount of central nervous system depressants—namely, amobarbital sodium and ethyl alcohol—required to produce the levels of the sedation thresholds. The assumption was that the psychological state of the organism determines, to a large extent, his reaction to the drug. The study also investigates the consistency in the effects of the two drugs, which were reported, separately, to produce some relatively comparable psychological changes. A study of the general effects of the drugs, qualitatively and quantitatively, on patterns of performance has also been attempted at the levels of the sedation thresholds.[7]

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Assistant Professor of Psychiatry, State University of New York College of Medicine, Downstate Medical Center, Brooklyn (3).

Method of Study

A group of 24 patients presenting varying degrees of "anxiety" were obtained from the psychiatric division of the Kings County Hospital Center. The subjects were selected on the following basis: The present admission was the first to a psychiatric hospital, and they were white males with an age range of 16 to 36 years. These subjects had never received any type of shock therapy and did not show any evidence of encephalopathy on physical, mental, and laboratory examinations. Clinically they presented a picture of predominantly psychoneurotic or character disorder. The group of subjects used was thus a selected one. This selectivity was felt desirable to secure—more or less—homogeneous sociopsychological patterns and to avoid as much as possible the interference of environmental, racial, and sex differences, which are known to be potential handicaps in studies of this nature. Such a group was also thought to reflect any existing differences or trends to a degree that would permit achievement of statistical significance. On each subject included in the study the following data were obtained:

1. Basic identifying information, including age, sex, race, degree of education, weight, and height.

2. An evaluation of the degree of his anxiety using three measures: clinical judgment,[3] the Figure-Drawing test,[8] and Taylor's Anxiety Scale.[14]

3. The sedation thresholds for amobarbital sodium and ethyl alcohol.

4. The performance on four psychological and psychomotor tests under the effects of amobarbital sodium, ethyl alcohol, and a no-drug condition. These tests are the sentence completion, the two-hand coordination, the steadiness, and the tapping speed test.[4-7]

5. Electroencephalographic recordings of the brain waves under the effects of amobarbital sodium, ethyl alcohol, and a "no-drug" condition.

This information was then subjected to analysis, considering each variable in an effort to clarify the relationship of the sedation threshold of one drug to that of the other and the relations between these thresholds and the degree of anxiety of the subject. An evaluation of the physiological,

psychological, and psychomotor changes at the sedation threshold levels was also undertaken.

A discussion of the technique of drug administration presupposes a definition of the sedation threshold. Shagass[9,10] defined the sedation threshold as an objective pharmacological determination which depended upon electroencephalographic and speech changes produced by intravenously given amobarbital sodium. The concept was introduced to measure manifest anxiety, and the sedation threshold was expressed in terms of grams of amobarbital sodium per unit of body weight required to produce the electroencephalographic and speech changes. For the purpose of this study, the concept of the sedation threshold has been expanded and slightly modified. It is the amount of amobarbital sodium in grains (grams), or of ethyl alcohol, in cubic centimeters, per 10 lb. of body weight that is required to produce slurred speech on two consecutive testing periods. This modification, as will be discussed later, has been found to meet the objectives of this investigation.

Technique of Drug Administration

The injection was preceded by routine examination of the physical condition. It was given only after the lapse of at least one and one-half hours after a meal to prevent gastrointenstinal and other disturbances. Two nurses assisted in this phase of the experiment. Their presence was thought advisable for the following purposes: to help with the preparation of the drug solution and with its administration under aseptic techniques; to record responses, and time at various stages of the experiment, and attend to the electroencephalogram, and to help with the administration of stimulants or other necessary measures in cases of emergency, such as respiratory distress or sudden drop of blood pressure. It also facilitates matters to have assistants in case a release of great affect occurs during or after drug administration.

The injection of amobarbital sodium was made up so that 1 cc. of sterile water contained 1.5 grains (0.10 gm.) of amobarbital sodium. The solution was freshly prepared before every injection. The drug was injected intravenously at the rate of 1 cc. per 40-second interval. This was followed by a 20-second period during which the subject was tested for slurred speech. The injection, followed by testing, was repeated in the same way until the subject had manifested slurring in his speech on two consecutive testing periods.

The apparatus that was employed to administer ethyl alcohol intravenously consists of a container for each of the following solutions: first, isotonic saline solution and, second, a solution of pure ethyl alcohol and isotonic saline solution in the proportions of 15 cc. of 95% ethyl alcohol to 85 cc. of isotonic saline solution. The tubes from these containers run to a Y-connector, which is equipped with a two-way stopcock, so that the solution in either bottle may be infused. With this type of apparatus the infusion can be administered by gravity. The whole apparatus was sterilized previous to injection, and the usual antiseptic precautions were taken in preparing the site of injection. The rate of flow was adjusted, using clamps, to 20 cc. per minute. By running the isotonic saline solution before and after the administration of the drug, the danger of thrombosis of the vein used is greatly reduced. Brain waves recorded during the injection of saline were also thought to have a value as a control for the effect of the insertion of the needle in comparing the saline effects with drug effects. The point of the sedation threshold, again, was that at which the subject manifested slurred speech on two consecutive testing periods.

The experiment was designed so that all possible permutations of the sequence of the three conditions (no-drug, amobarbital sodium, and ethyl alcohol) and the order of the four psychological and psychomoter tests were used, counterbalancing the effect of sequence, like learning experience, and that of order, like the duration of drug effect.

Results

This study, so designed as to meet the needs of several objectives, has revealed many findings of both importance and interest and has pointed out questions of considerable potential value in psychosomatic research. The present report will limit itself to the presentation and discussion of the findings related directly to the concept of the sedation threshold.

A. Correlation Between Sedation Thresholds for Amobarbital Sodium and Ethyl Alcohol.—A study of the relationship between the "sedation thresholds" for amobarbital sodium and for ethyl alcohol revealed a positive and significant correlation of $+0.58$ ($P<0.05$).* Thus, the subject who required a high dose of amobarbital sodium to get him to perform at a certain level of psychological functioning would, most likely, also require a high dose of ethyl alcohol to produce that state of psychological performance.

* All correlations presented in this paper are Pearson product-moment correlations.

TABLE 1.—*Correlation Between Sedation Thresholds for Amobarbital Sodium and Ethyl Alcohol and the Various Measures of Anxiety*

Measures of Anxiety	Sedation Thresholds	
	Amobarbital Sodium	Ethyl Alcohol
Taylor's Anxiety Scale	+0.22	+0.40 *
Clinical judgment	+0.64 †	+0.69 †
Figure-Drawing (diffuse-inferred)	0.00	+0.29
Figure-Drawing (obsess. compul.-hyst.)	+0.06	+0.12

* $P<0.05$.
† $P<0.01$.

B. Correlation Between the Measures of Anxiety and the Sedation Thresholds.—Table 1 shows that there is a significant positive correlation between the clinical judgment of anxiety, on the one hand, and the sedation thresholds for both amobarbital sodium and ethyl alcohol, on the other ($P<0.01$ in both conditions). The correlation between the Taylor Anxiety Scale and the sedation threshold for ethyl alcohol is also significant ($P<0.05$). There is no significant correlation, however, between either Taylor's scale and the sedation threshold for amobarbital sodium or the Figure-Drawing's two scales and the sedation thresholds for ethyl alcohol and amobarbital sodium.

C. Relationship Between Sedation Thresholds for Amobarbital Sodium and Ethyl Alcohol and Performance on Projective and Psychomotor Tests.—When exploring the clinical and experimental manifestations that could be used as criteria for the point of the sedation threshold, slurred speech, bilateral nystagmus, and electroencephalographic changes were considered. The bilateral nystagmus was not a constant finding in all patients. It developed only in few cases, where the subject had received a relatively high dose and went to sleep shortly after. It seemed reasonable to discard the bilateral nystagmus as an indication of the level of the sedation threshold on the grounds that it developed at a later stage than that required for the cooperation and adequate performance of the subjects on the psychological and psychomotor tests.

The electroencephalographic changes, though recorded and analyzed for other purposes in this investigation, were also eliminated as impractical criteria for the point of the sedation threshold. Some workers have indicated a very high correlation between the point of slurred speech and the point of inflection on the dosage-response amplitude curve on the electroencephalograms obtained under the influence of amobarbital sodium. They stated that the inflection point must occur within 80 seconds of the clinical observation of slurred speech.[10,11] In this study it became evident that, in order to obtain a reliable dosage-response curve of amplitude on the electroencephalogram in the absence of an automatic analyzer, every wave traced within a period of three to four minutes should be measured and included in the computation, since the reliability of samples selected randomly from the record proved to be quite low. To perform this task by the precise hand technique is extremely laborious. Thus the electroencephalogram as a criterion for the level of the sedation threshold was eliminated.

Since the only criterion for reaching the level of the sedation threshold was slurred speech, it was tested for reliability by running a correlation between the sedation thresholds for amobarbital sodium and ethyl alcohol and the performance on the projective and psychomotor tests. In this study we suppose that the level of the sedation threshold is a specific stage of psychological functioning. It is produced by a certain dose of the drug and is manifested by clinically observed slurred speech. A higher dose of the drug will then be assumed to be necessary to get the subject out of that specific stage produced by the sedation threshold, and psychological phenomena other than slurred speech will emerge. Also, the level of the sedation threshold has an effect on the psychological and psychomotor test battery. This effect is measured in per cent change in performance. If this assumption is correct, there

TABLE 2.—*Correlation* Between Sedation Thresholds for Amobarbital Sodium and Ethyl Alcohol and Change in Performance on Projective and Psychomotor Tests*

Projective and Psychomotor Tests	Change in Performance, % Change	Sedation Threshold	
		Amobarbital Sodium	Ethyl Alcohol
Two-hand coordination	Deterioration	−0.09	−0.12
Tapping speed	Deterioration	0.00	+0.06
Sentence completion (react. time)	Decrease	−0.10	−0.09
Steadiness	Improvement	+0.18	+0.04

* All correlations are insignificant.

should be no relationship between the doses of the drug producing the stages of the sedation thresholds and the change in performance on the tests, since the latter is a function of the stage of psychological functioning itself and not of the increased dose. Table 2 shows that the change in patterns of performance, as measured by per cent deterioration or improvement, is not significantly correlated with the doses of the drug that produced the effect. This finding holds true for all the tests used in this study under the effects of both amobarbital sodium and ethyl alcohol.

Comment

Both amobarbital sodium and ethyl alcohol are central nervous system depressants. Both drugs have been known to produce a certain amount of release of psychic tension, together with other behavioral manifestations. The release of psychic tension occurs after certain resistances that were present before the administration of the drug are overpowered by the drug effect. Owing to this property, both drugs have been used in investigations directed toward truth revealing. It would seem reasonable to assume that the nature or the strength of the resistances of one subject that would require a large dose of either amobarbital sodium or ethyl alcohol to evidence that phenomenon of release of psychic tension would most likely require a large dose of the other. This is the case in the present study. The correlation between the sedation threshold for amobarbital sodium and that for ethyl alcohol is significantly positive. This finding is of importance, since it indicates that submission to the effect of the drug is a function of the individual's particular psychic structure and function. This psychological state of the individual is most likely responsible for the consistency in effects of the two cerebral depressants which were studied separately and were found to produce some psychological phenomena in common to both.

The relationship between the sedation threshold and anxiety has been known and reported by several workers, and the concept is by no means a new one. The relationship of the sedation threshold to predominant hysterical or obsessional personality traits has been described.[9,10] The relationship of less manifest anxiety to predominant hysterical personality traits and of more manifest anxiety to predominant obsessional ones has also been described.[11,12] Eysenck,[2,3] in his factor analysis of data of large groups of subjects, derived three dimensions of personality, one of which was the introversion-extroversion continuum. He drew the attention to the extroverting effects of alcohol and amobarbital sodium. In another approach to personality investigation, that of Sheldon and Stevens,[13] high resistance to alcohol is listed as one of the criteria for cerebrotonic temperament. This would lead one to expect a high sedation threshold for alcohol in cerebrotonic persons, who are very similar to obsessional patients.

The study of the relationship between the various measures of anxiety and the sedation thresholds revealed a significant positive correlation between the clinical judgment of anxiety and the sedation threshold for amobarbital sodium and ethyl alcohol, while the other correlations were insignificant. Another observation that attaches more significance to this significant correlation—as a true, unbiased relationship—is the associate finding of a significant positive correlation between the

Taylor Anxiety Scale and the sedation threshold for ethyl alcohol. Thus the psychological state of the organism seems to determine the nature of the subject's reaction to the drug. Although it would be unfruitful endeavor to interpret the insignificant correlations between the rest of the measures of anxiety and the sedation thresholds, yet it would be of interest to note that all these correlations were positive and in the expected direction. This finding is not entirely consistent with some reports in the literature, where the measures of anxiety, through both clinical judgment and paper and pencil tests, were highly intercorrelated and significantly correlated with the sedation threshold of amobarbital sodium. The nonspecific and complex nature of anxiety, its various aspects that are measured by the different methods, and the validity and reliability of these methods are very likely issues that may have accounted for the controversial findings.

Summary

Twenty-four patients presenting varying degrees of anxiety were selected from the psychiatric unit of the Kings County Hospital Center. Each patient was subjected to evaluation for the degree of anxiety, utilizing several techniques. Each subject was then given a battery of psychological and psychomotor tests under three different conditions: no-drug, amobarbital (Amytal) sodium, and ethyl alcohol, at the levels of their sedation thresholds. There was a significant positive correlation between the sedation thresholds for amobarbital sodium and ethyl alcohol. These thresholds were also significantly correlated with the clinical judgment of anxiety. The sedation threshold for ethyl alcohol was significantly correlated with Taylor's Anxiety Scale. Since slurred speech was the only criterion for reaching the level of the sedation threshold, it was tested for reliability by studying the relationship between the sedation thresholds and the performance on the psychological and psychomotor tests. The per cent deterioration or improvement on the projective and psychomotor tests was found to have no significant correlation with the doses of the drug that produced the effect, thus asserting the reliability of the sedation threshold as a specific level of psychological functioning, with slurred speech as one of its clinical manifestations.

450 Clarkson Ave. (3).

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Blood Glutathione Levels in the Male Schizophrenic Patient

ANTHONY J. BARAK, Ph.D.; FRED L. HUMOLLER, Ph.D., and JOHN D. STEVENS, M.D., Omaha

In a recent review by Patterson and Lazarow [1] on the determination of reduced glutathione (GSH), the authors show that 10 different methods have been used in the analysis for glutathione. These authors state that the most widely used method is the iodometric titration method, and they go into some detail in describing this method, as well as the glyoxalase method and the alloxan "305" method.

Recently Martens [2] and Angel [3] and their associates have reported that the blood GSH levels in schizophrenic patients are significantly lower than those found in normal subjects. Previously Altschule et al.[4-6] had also reported that the patient with schizophrenia had levels of blood glutathione in or below his lower normal range

The GSH indexes (milligrams per 100 ml. of red blood cells) in schizophrenics reported by Altschule et al.[4-6] vary from 10 to 50, with an average value of 34. These values are very much lower than the levels reported by all other investigators [2,3,7-11] for normal subjects. Altschule's spread for schizophrenics is also below the levels for both acute and chronic schizophrenics reported by Angel et al.,[3] who cited a range of 39 to 85, with an average of 69, for acute schizophrenics and values of 51 to 87, with an average of 65, for chronic schizophrenics. Since Altschule and his group [4-6] reported so much lower GSH values for his schizophrenic group than other investigators found for normal controls, the present work was initiated to test the possible merit of the GSH index as an aid in the diagnosis of schizophrenics.

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From the Medical Research Laboratory and Neuropsychiatric Service, Veterans' Administration Hospital.

Method

Whole-blood GSH measurements were carried out by the iodometric titration method of Woodward and Fry,[7] as modified by Patterson and Lazarow.[1] In this method, the hematocrit of the

TABLE 1.—*Mean Glutathione Indexes Reported in the Literature for Normal Subjects and for Schizophrenic Patients*

Authors	Normal	Acute Schiz.	Chronic Schiz.	Method
Martens et al. [2]	(22)* 78±7		(20) 65±3.5	Nitroprusside
Angel et al. [3]	(12) 71 54-84	(13) 69 39-85	(11) 65 51-87	Same
Watson et al. [8]	(39) 71			Same
Altschule et al. [4]	(20) 34-75		(38) 10-50 †	Iodometric titration
Woodward & Fry [7]	(30) 68 ‡ 50-82			Same
Bichel [9]	(66) 68 ‡ ±4.39			Same
Seltzer [10]	(9) 81 ±6.70			Same
Boggs [11]	(13) 81 64-94			Same

* Figures in parentheses indicate number of subjects used in each series.
† Authors did not report whether patients were acute or chronic schizophrenics. Number of patients was estimated from graph.
‡ Authors reported GSH in milligrams per cent. Values in table are based on an assumed 30% hematocrit.

blood sample is determined by the capillary tube method; the blood is hemolyzed; the proteins are precipitated with sulfosalicylic acid, and an aliquot of the filtrate is titrated with a standardized solution of 2,6-dichlorophenolindophenol. This titration determines the level of reduced ascorbic acid in the blood and is used as a correction factor for GSH. To another aliquot of the filtrate an excess of 5% potassium iodide and 4% sulfosalicylic acid is added and the sample titrated with a standard potassium iodate solution (0.001 N), using starch as an indicator. The GSH content is calculated from the volume of potassium iodate used, and the GSH value is corrected for the ascorbic acid content of the blood. Using the hematocrit value, the GSH concentration is reported as the GSH index.

The method of Patterson and Lazarow [1] was found to be satisfactory in this laboratory when the three following changes were adopted: (*a*) In setting up the ascorbic acid method, the 2,6-dichlorophenolindophenol was standardized against 0.1 mg. of reduced ascorbic acid instead of the recommended 1 mg. The lower amount of ascorbic acid keeps the titration down to a convenient, workable volume. (*b*) Every precaution was taken to titrate for GSH immediately upon the addition of the 5% potassium iodide and 4% sulfosalicylic acid because of the instability of the hydriodic acid which is formed in this mixture. If this precaution is not taken, GSH values are lowered with time. (*c*) Edathamil disodium (disodium ethylenediaminetetraacetate [0.01 ml. of a 10% solution per milliliter of blood]) was used as an anticoagulant, in place of the oxalate solution which was previously used.

Since the quantitative estimation of the GSH index depends upon the results obtained in three separate determinations, that of hematocrit, ascorbic acid, and GSH, each with its own inherent error, the error of the over-all determination will be a summation of the separate errors. This fact may contribute to broadening the range of GSH indexes found in normal and in schizophrenic subjects, as reported in the literature and in Tables 2 and 3.

TABLE 2.—*Glutathione (GSH) Indexes in Schizophrenics*

Patient	No. of Determinations	Individual GSH Averages	Low-High
1	3	59	56–64
2	3	66	60–70
3	2	61	56–66
4	2	67	61–71
5	2	68	67–69
6	2	63	65–62
7	2	67	59–75
8	4	63	54–79
9	2	65	62–68
10	3	67	60–76
11	3	63	56–76
12	3	67	57–72
13	3	55	47–59
14	1	49	49
15	1	70	70
Total	36	Mean 63 S. D. ±8	

TABLE 3.—*Glutathione (GSH) Indexes in Controls*

Patient	No. of Determinations	Individual GSH Averages	Low-High
1	2	66	64–67
2	2	69	65–73
3	2	58	51–66
4	2	60	59–60
5	2	59	56–62
6	2	59	51–68
7	2	75	70–81
8	2	75	73–77
9	2	68	66–71
10	2	53	47–59
11	2	68	62–74
12	2	64	61–68
13	2	55	46–64
14	2	51	49–52
15	2	71	70–71
16	2	59	50–68
17	2	62	61–63
18	2	79	72–85
19	2	68	62–74
20	2	52	48–56
21	2	50	40–60
22	2	62	58–67
23	2	69	67–70
24	2	67	66–69
25	2	44	43–46
26	2	71	70–72
27	2	74	71–76
28	2	54	52–56
29	2	63	62–64
30	2	59	57–61
31	2	57	53–61
32	2	62	59–65
33	2	47	40–54
34	2	54	52–57
35	2	66	55–78
36	2	61	59–62
Total	70	Mean 62 S. D. ±10	

Material

During a period of about six weeks several GSH indexes were determined on each of 15 male hospitalized active schizophrenics and on 36 normal male subjects, known to be free from psychotic symptoms or systemic diseases. The repeated determinations (Tables 2 and 3) were carried out in order to determine the random fluctuations in the GSH index. None of the subjects used in this study had hematocrit values below 38%, since it is known that the red blood cell GSH content is elevated in anemia.[14]

Results

Using the above method, recovery studies with added GSH were performed. When GSH was added to the blood at the hemolysis step, the recovery was very poor. The exogenous GSH was quickly oxidized by the blood proteins, thus confirming the observations of Oberst [12] and Dohan and Woodward [13] on the disappearance of GSH

TABLE 4.—*Effect of Time on the Stability of GSH Index in Unhemolyzed Blood*

Temperature	Initial Determination	1 Hr.	2 Hr.	24 Hr.
Room (25 C)	54.5	54.5	54.0	48.5
Refrigerator (4 C)	....	55.0	50.0	52.0

under these conditions. On the other hand, when endogenous GSH was determined in one aliquot of the blood and total GSH was determined in another aliquot to which GSH was added at the precipitation step, an average recovery of 105% was obtained.

In clinical laboratory practice it is not always practical to determine the GSH level immediately after the blood is drawn. It became of interest, therefore, to determine the stability of GSH in unhemolyzed blood both at room temperature and at 4 C.

A large sample of hog blood was obtained from the slaughterhouse. One hour after the blood was collected an initial determination was made on the blood, which was then divided into two samples, one of which was kept at room temperature and the other at 4 C. GSH levels were carried out at 1-, 2-, and 24-hour intervals. Table 4 summarizes the results obtained from these analyses. It can be seen that blood can be stored in the refrigerator, or even at room temperature for a full day, without any appreciable loss in GSH.

The results obtained of the control and schizophrenic groups are summarized in Tables 2 and 3. The mean index in the schizophrenic group was 63, with a standard deviation of 8. The control group showed a mean GSH index of 62 ± 10 (Table 3). The difference between the control and the schizophrenic group is not statistically significant at the 5% level.

Comment

There seems to be a fairly good agreement among authors on the magnitude of the GSH index in normal subjects. At least the Tulane group,[2,3] using the nitroprusside (sodium nitroferricyanide) method, as well as Altschule and this laboratory, using the iodometric method, obtain comparable GSH indexes (Table 1). No such general agreement exists, however, with respect to the indexes found in schizophrenic patients. Thus, Altschule obtained consistently low indexes for his schizophrenic patients, whereas the other investigators report only an occasional low value.

In the present study only two indexes below 50 were found, and when the test was repeated on another day on one of the patients (Table 2, Patient 13), a value of 59 was obtained. The other patient (Table 1, Patient 14) was not available for repeated determinations.

The values obtained on normal controls and on schizophrenic patients are listed in Tables 2 and 3 and show clearly that there is no difference between the mean values for the two groups. These tables also show that the glutathione level in a given subject, either normal or schizophrenic, may fluctuate over a considerable range. The present study, therefore, fails to show any causal relationship between schizophrenia and the glutathione index. One must consider in evaluating these results that the method used in the present study, as well as the methods used by the other authors cited, are not specific for GSH, but at best will determine only nonprotein —SH groups. A specific enzymatic method for GSH has been described,[1] but, unfortunately, it is too tedious to be used for clinical studies.

Recent studies by Altschule et al.[5,6] have shown that beef pineal extracts injected into chronic schizophrenic patients over periods of from 50 to 90 days produce temporary clinical improvement. They state that during the period of injection and the period of improvement the blood GSH levels were increased. This increase was never greater than 10 GSH index units. In view of the wide variations within single subjects shown in this paper, and reported by other investigators, it is entirely possible that these changes in GSH may not have been due to pineal extracts, but that they

merely represent normal fluctuations within individual subjects or errors inherent in the method. While such extracts may produce clinical improvement in the patient, it is doubtful that such changes can be determined objectively by following changes in the GSH index.

Summary and Conclusions

In the present investigation certain aspects of blood glutathione were studied. Determinations of reduced glutathione (GSH) levels in schizophrenic patients and in normal subjects do not confirm the findings of other investigators that there is a difference of statistical significance between these two groups.

The present study shows that any differences that may exist between these two groups would be masked by the inherent error in the method, which depends on three separate determinations, each with its own individual error.

On the basis of these findings, it is difficult to see that the GSH determination would be of any assistance in diagnosing schizophrenia.

Veterans' Administration Hospital, 4101 Woolworth Ave. (5).

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Personality Differences and Continued Meprobamate and Proclorperazine Administration

E. LOWELL KELLY, Ph.D.; JAMES G. MILLER, M.D., Ph.D.; DONALD G. MARQUIS, Ph.D.;
R. W. GERARD, M.D., Ph.D., and LEONARD UHR, Ph.D., Ann Arbor, Mich.

Other publications[9,10] have reported behavioral effects of meprobamate, after a single dose of 800 mg. and after chronic administration of 800 mg. twice a day for 21 or 28 days. For comparison, the effects of similar chronic administration of 10 mg. doses of proclorperazine were also investigated. No adverse effects of these drugs were found on a wide variety of measurements of sensory, motor, and complex functions. In the study of chronic administration the subjects were also given a number of personality tests. This paper reports the results of an extensive experimental search for individual personality differences related to behavioral effects from continued administration of these drugs.

Method

The details of the procedure are reported elsewhere.[9,10] Briefly, 51 university students were tested, in a double-blind design, for the effects of meprobamate, proclorperazine, and placebo treatments. Dosages were 800 mg. of meprobamate twice daily, 10 mg. of proclorperazine twice daily, and matching placebos twice daily. Each subject took drugs for five consecutive periods of 21 or 28 days, receiving in the first period a placebo, in the second one of the drugs, in the third a placebo, in the fourth the other drug, and in the fifth placebo. Half the subjects received meprobamate in the second period and proclorperazine in the fourth; the other half received these treatments in the reverse order. A nurse and a physician were on call throughout the experiment to all subjects.

Subjects' performances on 51 behavioral variables were measured at the end of each period. The behaviors tapped covered a wide range, including driving skills, visual acuity, steadiness, tapping rate, characteristic tempos, perception tests, kinesthetic figural after-effects, line comparisons, and palmar perspiration. During the third period, while receiving placebos, all subjects were administered inventories measuring 68 personality variables.

Four standard personality tests were used to obtain 65 of the personality variables: the Minnesota Multiphasic Personality Inventory (MMPI)[7]; the California Personality Inventory (CPI)[8]; Edward's Personal Preference Schedule (PPS),[6] and Cattell's 16 Personality Factor Test (Form C) (16 PF).[3]

The MMPI yields 14 scores related to a wide range of neurotic and psychotic pathology. It has been used in many research projects and clinical situations.[5,7,8] The CPI is scored for 18 personality traits frequently found in normal people. A newer and less widely used instrument than the MMPI, it nevertheless shows promise of validly predicting neurotic diagnoses. The PPS gives objective scores for 16 basic personality needs used by Murray in interpreting the Thematic Apperception Test.[12] The PPS is one of the newest and methodologically most advanced objective psychological instruments. It is being used in a number of large-scale experiments started during the past year or two, with what appear to be promising results.[4] The 16 PF is the result of an unusually extensive program of personality test development conducted by Cattell over a period of years. The test measures 16 largely independent

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This study was conducted under the auspices of the Mental Health Research Institute and the Department of Psychology, University of Michigan.

Professor of Psychology and Director of the Bureau of Psychological Services, University of Michigan (Dr. Kelly). Professor of Psychiatry and Director of the Mental Health Research Institute, University of Michigan (Dr. Miller). Professor of Psychology and Chairman of the Department of Psychology, University of Michigan (Dr. Marquis). Professor of Neurophysiology, Departments of Psychiatry and Physiology, University of Michigan (Dr. Gerard). Research Associate, Department of Psychology and Mental Health Research Institute, University of Michigan (Dr. Uhr).

factors of personality, plus a "median score" which gives an over-all indication of a subject's personality. A great deal is known about the interrelationship of scales on this inventory, and numerous studies have indicated that 16 PF scores are related to occupation, attitudes, academic performance, pathology, and other criteria.

Three additional personality variables were included in our battery. The Miller Analogies Test (MAT) [23] was used as a measure of intelligence. This is a test of complex reasoning functions and is especially appropriate for advanced college and graduate students of high intelligence. The Blacky Analogies Test (BAT) [1] was used in conjunction with the MAT. In this test cartoon pictures of a puppy, depicting psychosexual behavior, may arouse disruptive anxiety when the cartoon material relates to the subject's own problems. In addition to the MAT and the BAT score, we computed a score of intellectual disruption as a result of arousal of anxiety by the Blacky pictures. The MAT and BAT were put into comparable units (standard scores) and their difference computed for each subject (the larger the resultant difference, the smaller the disrupting anxiety). Finally, the subject's sex was coded as a 69th variable.

Twenty of these personality variables were chosen (as outlined in the Appendix) for the search for relations between drug behavioral effects and personality characteristics.

Of the 51 behavioral variables, measured under the different drug treatments 40 were chosen, representing a characteristic array of behaviors that might be affected differentially by drug treatments, depending upon individual personality characteristics.

Three different scores were used, for each of the three possible treatment comparisons: (1) the difference between behavior measured after placebo administration and after meprobamate administration; (2) the difference between behavior measured after placebo administration and after proclorperazine administration, and (3) the difference between behavior measured after meprobamate administration and after proclorperazine administration. Three separate 40-variable intercorrelation matrices were computed, one for each of these treatment comparisons.

Results

Altogether, 2400 correlations were computed (20 by 40, or 800 for each of the three treatment comparisons). This large number cannot all be reported; so in Table 1 are indicated those correlations which were significant beyond the 1% level. Each of these indicates that the change in some specific behavior which was brought about by a drug was significantly different for those subjects who scored high on a given personality variable than for those who scored low.

TABLE 1.—*Correlations Significant Beyond the 1% Level Between Personality Variables and Drug Effects on Behavioral Variables, for Each of the Three Treatment Comparisons*

	Behavioral Variables Significantly Related *		
Personality Variable	Placebo Minus Meprobamate	Placebo Minus Proclorperazine	Meprobamate Minus Proclorperazine
1. Sex	4, 5, 35		5
MMPI			
2. Hypochondriasis	16		
3. Psychopath. Deviant			
4. Masculinity			
CPI			
5. Socialization	30		
6. Tolerance		37	3, 33, 40
7. Intellectual Efficiency	31	40	40
8. Flexibility	4		8
PPS			
9. Achievement	31		
10. Deference	24		
11. Exhibition	40		40
12. Autonomy			
13. Intraception			
14. Consistency			
16 PF			
15. Dominance			32
16. Bohemianism		27	10
17. Radicalism			6
18. Blacky Analogies			10
19. Miller Analogies	31		31
20. MAT-BAT		1, 25	

Behavioral Variables

1. Self-Rating—evaluation
2. Self-Rating—potency
3. Self-Rating—activity
4. How do you feel now—physically?
5. How do you feel now—psychologically?
6. How have you felt the last two weeks—physically?
7. How have you felt the last two weeks—psychologically?
8. Line judgment, % accuracy
9. Tapping rate
10. Preferred rate—slow
11. Preferred rate—fast
12. Preferred rate—subject set
13. Steadiness hole 3
14. Steadiness hole 5
15. Cancellation—first 3 pages
16. Cancellation—last 3 pages
17. Figural after-effects—before
18. Figural after-effects—after
19. Vertical phoria—far
20. Vertical phoria—near
21. Figural After-effects—difference
22. Lateral phoria—near
23. Depth perception
24. Visual acuity—far
25. Visual acuity—near
26. Flicker fusion—down
27. Apparent motion—up
28. Apparent motion—down
29. Driver Trainer—fast total time
30. Driver Trainer—variable total time
31. Driver Trainer—slow accuracy
32. Driver Trainer—fast accuracy
33. Driver Trainer—variable accuracy
34. Driver Trainer—slow reaction time
35. Driver Trainer—fast reaction time
36. Palmar sweat—rest
37. Palmar sweat—difference
38. Palmar sweat—active
39. Self-rating—lucky
40. Necker Cube

* Numbers refer to the following list of the 40 behavioral variables.

TABLE 2.—*Number of Significant Correlations Between Personality Variables and Drug Effects on Behavioral Variables, for Each of the Three Treatment Comparisons*

	Significance Level	
	5%	1%
1. Placebo-meprobamate	47	11
2. Placebo-proclorperazine	42	5
3. Meprobamate-proclorperazine	49	12
Average no. significant	46	9.3
No. to be expected by chance	40	8

It should be remembered in assessing these results that by chance alone eight of these correlations would be significant beyond the 1% level, and 40 significant beyond the 5% level, for each of the three matrices of 800 correlations. Table 2 shows the numbers of significant correlations obtained in each of the three correlation matrices.

Under the influence of *meprobamate, as contrasted with placebo,* a sex difference shows up on three behavioral variables: Men show a greater tendency than women (1) to feel relaxed physically, (2) to feel relaxed psychologically, and (3) to have a faster reaction time on the driving test at fast speed. For both men and women, high hypochondriasis scores (on the MMPI) are related to comparatively poorer performance on cancellation under meprobamate, while high socialization scores are related to comparatively longer total time on the driving test at variable (subject-controlled) speed. On the CPI, high Intellectual Efficiency is related to comparatively poorer accuracy on the driving test at slow speed, and high Flexibility is related to comparatively tenser physical feeling. On the PPS, high need to achieve in life is related to comparatively poorer accuracy on the driving test at slow speed; high need to defer to others is related to comparatively better visual acuity (distant), and high need to exhibit oneself to others is related to a comparatively greater number of Necker Cube reversals. A high Miller Analogies intelligence score is related to comparatively poorer accuracy on the driving test at slow speed.

Under the influence of *proclorperazine, as contrasted with placebo,* on the CPI, high Tolerance is related to a comparatively greater increase in perspiration when under stress, and high Intellectual Efficiency is related to a comparatively lower number of object-background alternations on the Necker Cube. On the 16 PF, a high Bohemianism score is related to one of the measures of a comparatively lower threshold of apparent motion. A high MAT-BAT score (an index of relatively small disruption of intellectual performance under anxiety-provoking conditions) is related to a comparatively lower evaluation of self, and to poorer visual acuity (near).

Twelve of the personality variable *vs.* behavioral variable correlations that were significant beyond the 1% level indicate contrasts in the effects of the two drug treatments. They will be reported as the effects of *proclorperazine, as contrasted with meprobamate.* There was one significant sex difference: Men showed a greater tendency than women to feel less relaxed psychologically. On the CPI, high Tolerance is related to a comparatively higher self-rating as to activity level, comparatively poorer accuracy on the driving test at variable speed, and comparatively slower apparent alternation of an object and its background (Necker Cube reversals). On other CPI variables, Intellectual Efficiency is related to comparatively fewer Necker Cube reversals, and Flexibility is related to a comparatively higher accuracy per cent on Line Judgments. On the PPS, need to exhibit oneself is related to comparatively fewer Necker Cube reversals. On the 16 PF, Dominance is related to comparatively greater accuracy on the driving test at fast speed; Bohemianism is related to a comparative speeding up of preferred tempo, and Radicalism is related to comparatively tenser physical feeling. A higher Blacky Analogies score is related to a comparative speeding up of preferred tempo. A higher Miller Analogies intelligence score is related to comparatively greater accuracy on the driving test at slow speed.

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4. Masculinity			
CPI			
5. Socialization	30		
6. Tolerance		37	3, 33, 40
7. Intellectual Efficiency	31	40	40
8. Flexibility	4		8
PPS			
9. Achievement	31		
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14. Consistency			
16 PF			
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35. Driver Trainer—fast reaction time
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TABLE 2.—*Number of Significant Correlations Between Personality Variables and Drug Effects on Behavioral Variables, for Each of the Three Treatment Comparisons*

	Significance Level	
	5%	1%
1. Placebo-meprobamate	47	11
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It is of interest that two of the personality variables examined yielded unusually large numbers of significant correlations with differences in behavioral variables. Under meprobamate, as contrasted with placebo, masculinity was related to reporting more relaxed psychological and physiological feelings, and to faster driving reaction times. CPI Tolerance (a variable highly related to emotional stability, as shown in the Appendix) was related to greater increase in palmar sweat difference, higher self-ratings as to activity, poorer driving accuracy, and fewer Necker Cube reversals, with proclorperazine than with placebo or with meprobamate. Thus, the two personality variables that the present study indicates are most likely to be related to differential effects of drugs like those used in this investigation are Masculinity-Femininity and Stability-Anxiety.

Over-all, the present analysis indicates that, within our normal population, objectively measured individual personality differences have no dependable relation to the effects of either meprobamate or proclorperazine on the wide range of behaviors tested. The few significant relations uncovered should be considered as indicating promising hypotheses for further studies devoted explicitly to them, since chance fluctuations alone could account for most, if not all, of the findings of this study.

Summary

Individual personality differences among 51 normal subjects related to behavioral effects from continued administration of meprobamate or proclorperazine have been investigated. Fifty-one behavioral scores were obtained for all subjects, and a representative group of forty of these scores was selected for the present analysis. For each of the same subjects 69 scores were obtained on objective personality tests. Of these 69 personality scores, 20 were selected for the present analysis, on the basis of a factor-analytic study.

Three treatment comparisons were made between (1) meprobamate and placebo, (2) proclorperazine and placebo, and (3) proclorperazine and meprobamate. For each of these three treatment comparisons, correlations were calculated between each of the 20 selected personality variables and all of the 40 selected behavioral scores. Only those 28 of the 2400 calculated correlations which achieved significance beyond the 1% level are discussed. By chance alone 24 of these correlations would be significant at the 1% level. Each significant correlation has interest as a potentially fruitful hypothesis for future experimentation.

The present study has demonstrated no adverse effects of continued administration of double the standard dose of meprobamate on driving skills, perception, or any of a wide range of objectively measured behaviors either for normal subjects as a whole or for such subjects characterized by any of the personality variables studied. Similar results were obtained with proclorperazine.

Appendix

Sixty-six of the personality variables (all but MAT, BAT, and MAT-BAT) were subjected to a factor analysis in an effort to determine the primary independent factors or characteristics being measured by the many personality scores. Discovering these unrelated factors clarifies the occasional partial relationships which exist among several different, but not entirely different, measures. Objective mathematical criteria for placing the factor structure (in this study, the "quartimax" rotation) give the clearest-cut possible picture of how the factors underlie the tests. Further, the "factor loading" of each test on each factor gives an indication (similar to a correlation coefficient) of the degree to which that test measures that factor.

We also calculated the communality for each variable, a measure of the extent to which it measures something different from any of the factors. It is the sum of the squares of the correlations of the variable with each of the factors. If the variable measured only aspects of behavior identified

TABLE 3.—*The Twenty Personality Variables Selected for Correlation with Drug Effects on Behavioral Variables; with Factor Loadings on the Four Extracted Factors*

Personality Variable	Factor Loadings				Communality
	F. I	F. II	F. III	F. IV	
1. Sex (F. II)	−0.13	0.66	0.05	−0.01	0.45
MMPI					
2. Hypochrondriasis (F. III)	−0.09	0.04	0.69	0.09	0.50
3. Psychopathic Deviate	−0.18	0.31	0.23	0.32	0.28
4. M-F	−0.02	−0.37	0.22	0.02	0.19
CPI					
5. Socialization (F. IV)	0.26	−0.19	0.12	−0.58	0.46
6. Tolerance (F. I)	0.83	0.17	0.13	0.02	0.74
7. Intellectual Efficiency (F. I)	0.79	−0.03	0.03	0.08	0.63
8. Flexibility (F. II)	0.23	0.57	0.19	0.33	0.52
PPS					
9. Achievement	−0.07	−0.26	−0.07	0.25	0.20
10. Deference	0.16	−0.26	0.25	−0.18	0.19
11. Exhibition	0.03	0.17	−0.04	0.19	0.07
12. Autonomy (F. IV)	−0.02	0.19	0.08	0.54	0.33
13. Intraception	0.12	−0.05	−0.09	0.20	0.07
14. Consistency	0.11	−0.03	0.24	0.09	0.08
16 PF					
15. Dominance	−0.17	−0.01	−0.26	0.26	0.17
16. Bohemianism	0.00	−0.09	0.11	0.13	0.04
17. Radicalism	0.07	−0.11	0.26	0.28	0.16
Variables Not Included in Factor Analysis					
18. Blacky Analogies (placebo)					
19. Miller Analogies					
20. Blacky-Miller Analogies					

by factors, its communality would sum to 1.00; therefore, the smaller the communality less than 1.00, the more it is measuring something unrelated to any of the factors.

The factor analysis was done for two reasons: (*a*) If all 66 variables had been independently correlated with each of the measures of behavior change, more than 10,000 correlations would have resulted, far too many for meaningful interpretation; and (*b*) discovery of the factors in this group of tests, never before administered together to a single group of subjects, is in itself of scientific interest.

(The number of subjects included in this factor analysis was 89, 38 of the university students in addition to those used in our primary study being given the same tests by Dr. W. J. McKeachie, who is using the results also as a basis for choosing assessment instruments in an investigation of his comparing the effectiveness of different teaching methods.)

Our computations extracted four independent factors: (I) Stability *vs.* Anxiety; (II) Masculinity *vs.* Femininity; (III) Pathological Emotional Sensitivity, and (IV) Independence of Thought. A large number of variables were unrelated to any of these factors, indicating that these variables are additional unique dimensions, different from any of the others. The personality variables finally chosen for correlation with the behavioral measures in this study included 7, each highly loaded on one of the factors (good factor indices), and 10 at the other extreme, with unusually low loadings (so representing unrelated dimensions). In addition, the MAT, BAT, and MAT-BAT scores were used, giving altogether 20 personality variables used in the study. Table 3 shows these variables and their factor loadings.

Dept. of Psychology, University of Michigan.

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Continued Meprobamate and Proclorperazine Administration and Behavior

E. LOWELL KELLY, Ph.D.; JAMES G. MILLER, M.D., Ph.D.; DONALD G. MARQUIS, Ph.D.; R. W. GERARD, M.D., Ph.D., and LEONARD UHR, Ph.D., Ann Arbor, Mich.

In a previous study it was found that meprobamate had no adverse effect on the performance of normal subjects as measured by several tests of sensory, motor, and complex functions. The dose was 800 mg., which is twice the usual clinical dose. The tests were designed to sample several important everyday tasks, such as driving an automobile, that might be affected by a tranquilizer. Out of 21 variables measured, palmar sweat was the only one that showed a statistically significant change with meprobamate.

The present investigation extends in several directions the earlier study of the effects of meprobamate on behavior. First, instead of a single dose, there was chronic administration of the drug. Because most patients use a tranquilizer for a prolonged period, it is clearly important to test for any possible effects of continued use. Second, many more behavioral tests were used. Extensive sampling of many different kinds of behavior is essential to a thorough understanding of drug effects. Finally, another tranquilizing drug, proclorperazine, was also used. Comparison of meprobamate with another drug recommended for the same clinical conditions offers the possibility of a finer differentiation of effects.

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This study was conducted under the auspices of the Mental Health Research Institute and the Department of Psychology, University of Michigan.

Professor of Psychology and Director of the Bureau of Psychological Services, University of Michigan (Dr. Kelly). Professor of Psychiatry and Director of the Mental Health Research Institute, University of Michigan (Dr. Miller). Professor of Psychology and Chairman of the Department of Psychology, University of Michigan (Dr. Marquis.) Professor of Neurophysiology, Departments of Psychiatry and Physiology, University of Michigan (Dr. Gerard). Research Associate, Department of Psychology and Mental Health Research Institute, University of Michigan (Dr. Uhr).

Method

Subjects.—The subjects were university students who volunteered for the experiment. All were paid for their participation. There were 30 men and 30 women subjects at the beginning of the experiment, but 9 of them withdrew because either of illness unrelated to the drug treatment or of departure from the university. This left a group of 51 (26 men and 25 women) for whom the testing was completed. A nurse and physician were on call to all subjects throughout the experiments. No side-effects other than drowsiness were reported.

Dosage and Treatment.—The meprobamate dosage was 800 mg. twice a day; the proclorperazine dosage was 10 mg. twice a day. The drugs or a placebo was distributed daily by research assistants, who also ascertained that the pills were actually taken. The pills were placed in sealed envelopes by assistants hired specifically for this job. Neither subjects nor experimenters knew which medication was being taken. The objective nature of the tests also minimized any bias that might have resulted from knowledge or conjecture about the treatment.

Each subject was tested five times with the entire battery: the first time at the beginning of the experiment; the second time 28 days later; the third time after another 28 days; the fourth time after 21 additional days, and the fifth time after 10 more days. The entire experiment therefore covered a four-month period.

Two randomly chosen groups of 30 subjects, each containing 15 men and 15 women, were run through two orderings of drug treatments, designed to balance out any practice effects. The orderings of treatment are shown in Table 1. As indicated in the Table, the subjects were tested after chronic dosage of meprobamate or prochlor-

TABLE 1.—*Ordering of Drug Treatments*

Duration of Treatment, Days	Group I N=30	Group II N=30
1 to 10	Placebo	Placebo
28	Meprobamate	Proclorperazine
28	Placebo	Placebo
21	Proclorperazine	Meprobamate
10	Placebo	Placebo

perazine for either 28 or 21 days, depending on which experimental group they were in.

The Test Battery.—The test battery consisted of 12 different kinds of tests, which yielded 51 scores. These tests, together with the scores obtained on each one, are described below.

A. Driver Test (8 scores): The American Automobile Association's Auto Trainer was used. The trainer consists of two parts: the complete controls of a conventional-shift automobile and a treadmill-like belt, about 10 ft. long, painted to resemble a winding road, which extends from the front of the control unit. A model car, operated by the subject, rests on the belt. The subject's job is to keep the car on the road and to brake the car whenever a red light appears. A more complete description of this apparatus is given by Marquis et al.[6]

The subjects were given trials as follows: 20 revolutions of the belt at a fixed low speed, 20 revolutions at a fixed high speed, and 20 revolutions at a speed controlled by the subject. Six reaction-time determinations were interspersed irregularly through the first two trials.

Accuracy, or proficiency, of driving in this situation is measured in terms of the ability of the subject to keep the car on the road. Four accuracy scores were obtained: at the fixed low speed, at the fixed high speed, at the variable speed controlled by the subject, and at the difference between fixed low and high speeds. A "speed" score was also obtained, indicating the time required for each trial when the subject was controlling his own speed. During this phase of the test the subject was asked to drive as rapidly and as accurately as he could. In addition, a derived score was also figured—the ratio of the difference between the accuracy score at low fixed speed and the accuracy score at subject-controlled speed, divided by the time score. This speed-accuracy ratio, which indicated the degree to which speed was sacrificed for accuracy, or vice versa, may be interpreted as a measure of judgment. The eight scores on the Driver Test thus consisted of four accuracy scores, one speed score, one judgment score, and two reaction-time scores.

B. Palmar Perspiration (3 scores): To secure measures of autonomic response as a possible index of anxiety, two determinations of palmar perspiration were made. The technique is an adaptation of one used by Mowrer,[7] in which the subject's thumb is swabbed with a solution of ferric chloride. A small square of paper, soaked in a 5% aqueous solution of tannic acid and allowed to dry, is taped to the subject's thumb for a 15-minute test period. Details of procedure and scoring are given by Marquis et al.[6]

Palmar perspiration was determined twice: first, at rest, while the subject sat quietly before testing was begun; and again while the subject was engaged in the comparatively stressful task with the driver-training apparatus. A third score was derived from these two variables by subtracting the score at rest from the score during driving, to give a measure of the increase in perspiration from the normal level under stress.

C. Steadiness Test (5 scores): This is an adaptation of the Whipple Steadiness Test[8] and consists of a test panel containing a series of five holes, decreasing in size from $\frac{7}{16}$ to $\frac{3}{16}$ in. The subject inserts a round metal stylus $\frac{1}{8}$ in. in diameter into each of the holes and tries to hold it there for 15 seconds without touching the sides of the hole. One trial on each of the five holes was given. Scores are obtained by counting the total amount of time that the stylus was in contact with the edge of the hole.

D. Vision Tests (10 scores): Vision tests were conducted using the Bausch & Lomb Optical Company's master-model Ortho-rater, a device designed to test various visual functions with distance and illumination controlled.[6]

Acuity was determined for both far and near vision; depth- and color-perception scores were determined for distant vision only. Vertical and lateral phorias for both near and far vision were also measured. Phoria scores indicate the relative posture or muscular balance of the eyes in relation to each other under conditions of controlled accommodation. A perfect vertical phoria score indicates that the horizontal midlines in both the right and left visual fields are in the same axis. A perfect lateral phoria score indicates the same for the vertical midline. Plus vertical phoria scores indicate orthophoria; minus scores indicate hyperphoria or hypophoria. Plus lateral phoria scores indicate orthophoria; minus scores indicate exophoria or esophoria.

E. Kinesthetic Figural After-Effect (3 scores): This apparatus, developed by Köhler and Wallach,[8] was used to follow up evidence that kinesthetic figural after-effects are indications of personality disorders. Eysenck found that hysterical patients, as compared with dysthymic (anxious) patients, more quickly developed figural after-effects, which were stronger and more persistent.[9] Klein and Krech found much the same effects for brain-injured patients as compared with normal subjects.[4]

The apparatus consists of three unpainted, smoothed hardwood blocks; the standard object,

the test object, and the comparison scale. The standard object is 1½ in. wide, 6 in. long, and 1 in. deep. The test object is 2½ in. wide, 6 in. long, and 1 in. deep. The comparison scale is 30 in. long and tapers from ½ to 4 in. in width. All three blocks have movable riders, which serve to keep the subject's thumb and forefinger correctly placed as he moves these fingers back and forth along the length of the block. The subject is blindfolded before the apparatus is uncovered. He sits with the comparison scale stretching away in front of his left hand and the standard object in front of his right hand. The experimenter positions the subject's thumb and forefinger on the two blocks.

The subject is instructed to move his left hand until he feels that he has found the point on the comparison scale that is the same width as the standard object. The position of the fingers on the comparison scale is indicated by a marker centered between the movable riders so that it points to a ruler fixed to the top of the block of wood. This task is repeated four times, the position of the comparison scale being varied systematically for each new comparison. Then the test object is placed in front of the subject's right hand, his thumb and forefinger positioned in the riders, and instructions given to rub the block back and forth for 30 seconds. The subject is again presented with the comparison scale, and the standard object and the four judgment trials are repeated. Three scores are obtained: (1) original judgment, (2) after-effect judgment, and (3) after-effect decrement, or difference in judgment from (1) to (2).

F. Flicker Fusion (2 scores): This was measured on a Lafayette Flicker Fusion Apparatus No. 1202, using Type 30N neon bulbs. Scores on five ascending trials, in which the on-off frequency was continuously increased by the experimenter, and on five descending trials, in which the frequency was continuously decreased, were averaged into two scores on each test: mean ascending flicker-fusion threshold and mean descending flicker-fusion threshold.

G. Apparent Motion (2 scores): The Lafayette Flicker Fusion Apparatus was also used to measure apparent motion. Scores on mean ascending threshold and on mean descending threshold were obtained.

H. Preferred Tempo Tests (6 scores): Measures of preferred tempos and characteristic rates were made in an attempt to get at behavioral concomitants of the somnolence and slowing that are occasionally reported as side-effects of tranquilizers. First, subjects were instructed to swing their arms back and forth at a rate that felt comfortable, as when walking. Next they were told to imagine they were in a hurry to get somewhere important. Finally, they were asked to set an electric metronome to the tempo they liked best. A fourth measure was derived by taking the difference between the "comfortable" and the "hurrying" tempo.

Tapping rate was measured as the average of two 30-second trials for which the subject was told: "Tap as fast as you can." Tapping was done on a standard telegraphic key and recorded on an impulse counter.

Rate of reversal of figure-ground perception was measured by averaging the number of subjectively apparent reversals during two one-minute trials of a Necker Cube drawn on a card. If stared at, the cube appears first to have one of its surfaces forward; then it shifts to another, then back to the first, and so on.[3,8]

I. Continuous Attention (2 scores): This test is an adaptation for paper-and-pencil administration of the Continuous Performance Task developed by Rosvold et al.[10,11] Six pages of 100 lines each of 10 random-letter groups, in half of which an "E" was embedded, formed the test material. The subject was instructed to write a plus next to lines that contained "E's," and a zero next to lines that did not. He was further told to respond at a constant rate—one line to each beat of a metronome, set a second apart. Subjects were started at the top of the first page, at the bottom of the second page, at the top of the third page, etc. Separate accuracy scores were obtained for the first three and for the last three pages.

J. Judgment-of-Lines Test (3 scores): Taken from Cattell's Objective-Analytic Test Battery,[2] this test is said to be an objective measure of general anxiety. Instructions are to mark an X to show which of two lines is longer than the other, unless the two are of equal length. This is a timed test, in which 30 seconds is allowed for each of four pages of lines to be compared, each page containing 20 pairs of lines. Three scores are obtained: completions, accuracy, and per cent accuracy.

K. Self-Rating Forms (3 scores): At the beginning of each testing period two self-rating forms were filled out by the subject. First, he was asked to rate himself, using a modification of the Semantic Differential,[9] on adjectives with high loadings on the three semantic factors identified by Osgood: (1) evaluative, (2) activity, and (3) potency. This gave three self-perception scores, plus a fourth score on self-rating as "lucky-unlucky."

L. Self-Report Questions (5 scores): Five self-report questions were also given.

1. How tense or relaxed are you physically?
2. How tense or relaxed are you psychologically?
3. In general, how have you felt during the last two weeks physically?
4. In general, how have you felt during the last two weeks psychologically?
5. How many hours did you sleep last night?

TABLE 2.—*Differences Between Scores on the Fifty-One Behavioral Variables for Combinations of the Three Experimental Conditions*

Tests	Differences Between Scores in Standard Deviation of Placebo Action		
	Meprobamate vs. Placebo	Proclorperazine vs. Placebo	Meprobamate vs. Proclorperazine
A. Driving tests			
Accuracy			
1. Fixed low speed	−0.02	+0.10	−0.13
2. Fixed high speed	−0.04	−0.06	+0.02
3. Variable speed	−0.04	+0.11	−0.15
4. Diff between low and high speed	+0.03	+0.28 *	−0.25
Time			
5. Variable speed (slower)	+0.20	+0.36 *	−0.16
Reaction time			
6. Fixed low speed	+0.02	−0.01	+0.03
7. Fixed high speed	−0.08	+0.13	−0.21
8. Judgment	+0.03	−0.02	+0.05
B. Palmar perspiration test (less)			
1. At rest	−0.08	−0.25	+0.16
2. Under stress	−0.04	−0.03	−0.01
3. Diff. between rest and stress	+0.12	+0.17	−0.05
C. Steadiness test			
1. Largest hole	+0.13	−0.01	+0.14
2. Next-to-largest hole	+0.19 *	−0.10	+0.29
3. Medium hole	+0.09	+0.16	−0.07
4. Next-to-smallest hole	−0.04	−0.09	+0.05
5. Smallest hole	+0.16	−0.11	+0.28
D. Visual tests			
1. Depth perception	+0.08	+0.13	−0.04
2. Color perception	−0.06	+0.13	−0.19 *
Acuity			
3. Distant	−0.05	−0.10	+0.05
4. Near	0.00	−0.11	+0.11
Vertical phoria			
5. Distant	+0.13	0.00	+0.13
6. Near	−0.15	−0.30 *	+0.15
Lateral phoria			
7. Distant	0.00	−0.13	+0.13
8. Near	+0.06	+0.02	+0.04
E. Figural after-effect test			
1. Original judgment	−0.01	−0.05	+0.05
2. After judgment	+0.03	−0.03	+0.06
3. After decrement (greater)	−0.04	−0.02	−0.02
F. Flicker-fusion test			
1. Ascending	−0.08	0.00	−0.08
2. Descending	−0.06	+0.03	−0.09
G. Apparent motion test			
1. Ascending	+0.10	−0.07	+0.17
2. Descending	−0.03	−0.19	+0.16
H. Preferred tempos test			
Walking rates (faster)			
1. Comfortable	+0.36	−0.15	+0.52 *
2. In a hurry	0.00	−0.13	+0.13
3. Subjective set	+0.07	0.00	+0.06
4. Diff., comf-hurried	−0.04	−0.02	−0.02
5. Tapping rate	+0.09	+0.09	+0.01
6. Figure-ground reversal rate	+0.02	+0.10	−0.08
I. Continuous attention test			
E cancellation			
1. First half	+0.02	+0.13	−0.12
2. Second half	+0.09	+0.10	−0.01
J. Line-judgment test			
1. Completion	−0.31 *	−0.20	−0.12
2. Accuracy	−0.25 *	−0.29 †	+0.04
3. % accuracy	−0.20	−0.26 *	+0.06
K. Semantic Differential test			
1. Evaluative factor	+0.10	−0.13	+0.13
2. Activity factor	+0.20	−0.04	+0.24
3. Potency factor	+0.21	+0.08	+0.12
4. Lucky-unlucky	−0.13	0.00	−0.13
L. Self-report test			
At present			
1. Psychological	−0.30	+0.10	−0.40 †
2. Physiological	−0.42 *	−0.11	−0.32
Past two weeks			
3. Psychological	−0.05	+0.05	−0.09
4. Physiological	+0.14	+0.10	+0.05
5. Hr. slept prev. night (longer)	+0.22	+0.29	−0.08
Total differences significant beyond 5% level	4	6	3
Total expected by chance	2.6	2.6	2.6

* Significant at the 0.05 level.
† Significant at the 0.01 level.

Results

The results are shown in detail in Table 2. The data were analyzed in the following way. Scores for all subjects on each of the tests taken after one of the drug treatments were averaged. These average scores were then used to make the three possible comparisons of the three treatments: (1) meprobamate *vs.* placebo; (2) proclorperazine *vs.* placebo; and (3) meprobamate *vs.* proclorperazine.

Mean differences and critical ratios were computed. The mean differences shown in Table 2 are expressed in standard score units. In other words, they are based on the standard deviation of the distribution of raw scores under the placebo condition. The second set of "placebo scores," obtained midway between the two "drug scores," was used as the base-line placebo condition. It was decided to use the scores from the second period because half the subjects took each drug before, and half after, this period. It was not only closest in time to both drug administrations but also, of the three placebo periods, most similar to the drug periods in other ways.

A plus score in Table 2 represents a difference in which the first-listed treatment is more favorable, and a minus score, one in which it is less favorable. For example, the score of +0.03 for Judgment on the Driving Test means that there was a difference of 0.03 standard score unit between

meprobamate and the placebo and that the subjects were very slightly better with meprobamate. If the "favorable" direction is not obvious, it is indicated in parentheses immediately after the name of the test; for example, "less" palmar perspiration is considered the more favorable score.

Inspection of Table 2 shows that for 141 of the scores there was no difference in performance under the three conditions. Only 10 of the mean difference scores are statistically significant at the 0.05 level of confidence and only 2 scores are statistically significant at the 0.01 level of confidence. Since a total of 153 tests of significance were computed, chance alone would yield 7.6 significant differences at the 0.05 level and 1.5 significant differences at the 0.01 level.

It is, of course, not possible to judge which of such differences may be replicable and which are simply due to chance. Under these circumstances the best general conclusion to be drawn from the data is that meprobamate has no adverse effect on a wide variety of performances. The same conclusion is true for proclorperazine, and there are also no clear differences between meprobamate and proclorperazine. Testing a new population of subjects on the 12 variables which showed significant differences in this study is the only way to tell whether these differences are dependable.

Comparison of Chronic and Acute Administration.—All the tests used in the first study of the behavioral effects of meprobamate were included in the present study on subjects drawn from a somewhat similar population, allowing for a comparison between the effects of meprobamate given in a single 800 mg. dose and of a continuous regimen of 21 or 28 days on 800 mg. per day. Table 3 presents these comparisons of acute *vs.* chronic administration of meprobamate for all of the variables measured in both studies. The difference between performance under meprobamate and that under placebo was computed for each study and the significance of the difference between these two differences evaluated. To give some indication of the magnitude of these differences, they are expressed in terms of the standard deviation of placebo action in the acute study. A plus score represents a more favorable change in performance from placebo to meprobamate under acute administration; a minus score indicates more favorable change in performance from placebo to meprobamate under chronic administration.

TABLE 3.—*Comparison of Differences Between Scores Under Placebo and Under Meprobamate from Acute to Chronic Administration Conditions*

Test	Differences Between Differences in Standard Deviations of Placebo Action, from Placebo to Meprobamate, Acute to Chronic Administration
A. Driving tests	
Accuracy	
1. Fixed low speed	+0.19
2. Fixed high speed	+0.11
3. Variable speed	+0.08
Time	
4. Variable speed	−0.11
5. Judgment	+0.05
Reaction time	
6. Fixed low speed	−0.35
7. Fixed high speed	−0.53
B. Palmar perspiration test (active)	−0.31
C. Steadiness test	
1. Largest hole	+0.05
2. Next-to-largest hole	+0.01
3. Medium hole	+0.03
4. Next-to-smallest hole	−0.13
5. Smallest hole	−0.26
D. Visual tests	
Depth perception	
1. Distant	0.00
Acuity	
2. Distant	+0.05
3. Near	+0.09
Vertical phoria	
4. Distant	−0.17
5. Near	+0.38 *
Lateral phoria	
6. Distant	+0.12
7. Near	−0.18

* The probability is less than 1 in 20 that this result could have occurred by chance.

On only one (vertical phoria—near) of the 20 variables that were measured in both meprobamate studies was there a significant difference in drug effect between the acute and the chronic administration. Since 1 of 20 tests would be expected by chance alone to be significant at this level (0.05), there is little reason to believe, on the basis of the comparisons that can be made between these two studies, that there is any statistically significant difference in the behaviors tested between the effect of a single and that of repeated doses of meprobamate.

Summary

Fifty-one scores were obtained on a battery of behavioral tests measuring psychomotor performance (simulated driving, steadiness), visual acuity, anxiety, and personality variables, after chronic administration of meprobamate, proclorperazine, and placebo to 51 normal subjects. Chance fluctuations alone can probably account for most, if not all, of the statistically significant differences obtained between performances under the experimental conditions.

Meprobamate appears to have no adverse effects on a wide variety of performances measured in this study. The same is true for proclorperazine. The present study confirms and extends the findings of a previous investigation on the behavioral toxicity of meprobamate. No dependable impairment in driving skills as measured by our tests appeared under either acute or chronic administration of meprobamate.

Mr. and Mrs. Gershom Morningstar, Mr. Robert Lindy, and Mr. David Wolsk served as research assistants in this investigation.

Dept. of Psychology, University of Michigan.

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ADDENDUM

After the present paper went to press, our attention was called to the recent article by T. A. Loomis and T. C. West, Comparative Sedative Effects of a Barbiturate and Some Tranquilizer Drugs on Normal Subjects (*J. Pharmacol. & Exper. Therap.* 122:525-531, 1958). They found that meprobamate, chlorpromazine, and secobarbital produced a significant impairment of performance on a simulated automobile-driving apparatus. Phenaglycodol and placebo did not. Loomis and West maintained that they obtained positive results (which we, as well as other investigators, did not) because, among other things, their subjects were more thoroughly trained and their driving task was more difficult. These factors are quite possibly of real importance. Certain questions, however, may be raised about their study: 1. What is the general significance of a research in this field with only eight subjects, especially since analysis of variance showed a markedly significant difference among subjects ($P<0.001$) and interactions between drugs and subjects were not reported? 2. Why was the order of administering the drugs to different subjects not randomized? 3. Does not their procedure of summing three mean per cent deviations from control without altering the base from 100 produce a misleading impression of the magnitudes of the drug effects? 4. In attempting by such methods to evaluate drug effects on driving, does one wish to study "peak" performance or "typical" performance?

Homosexuality in College

A Preliminary Report of Data Obtained from One Hundred Thirty-Three Students Seen in a University Student Health Service and a Review of Pertinent Literature

MATHEW ROSS, M.D., Los Angeles, and FRED MENDELSOHN, San Francisco

This report, a preliminary one, of a portion of a continuing research project on homosexuality as seen in the psychiatric section of a university student health service presents data in two areas where perusal of the literature on homosexuality reveals they are either lacking or minimal: (1) some characteristics of homosexuals in a college population and (2) treatment results. Most survey-type studies have dealt with prison and mental hospital inmate population; to our knowledge only one study has dealt specifically with a university student homosexual population, and another indirectly. Previously, little, if any, effort to assess the efficacy of therapy with a group of homosexuals as compared with that in a nonhomosexual psychiatric control group has been made.

The Student Health Service at the University of California at Los Angeles provides outpatient psychiatric facilities to all students who are regularly enrolled. The records of the psychiatric division are separately kept, and the reputation of the clinic for maintaining the ethical confidentiality of the doctor-patient relationship insofar as student, administration, and students' families are concerned, is attested to by the increasing use of the facility since its inception, as well as the high percentage of self-referrals.

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Fourth-year student, Stanford University School of Medicine (Mr. Mendelsohn).

Department of Psychiatry, Student Health Service, University of California at Los Angeles, and Department of Psychiatry, University of California School of Medicine at Los Angeles.

Selection of Cases and Incidence

Selection of cases in prior studies has created a problem.

Curran,[1] for his analysis of 100 male homosexuals seen in private practice in England, confined himself to cases in which homosexuality was either the presenting problem or a major part of the diagnostic formulation. All of these patients were consciously aware of their homosexual propensities and/or had indulged in homosexual acts with others.

Glover[2] selected for study 12 male college students who were "overt performers of deviant sex practices with their own sex by reason of personal choice, without coersion, with enjoyment—who frequently sought the haunts and company and engaged in the activities of other homosexuals." This University of Wisconsin group all felt they were different from others of their age group in childhood and that they were definitely in a different social category after puberty. While none of them attributed their state to any deviant pattern in their immediate family, only a few knew their genealogy beyond their parents, and none knew any details of the sexual patterns of their parents. In their immediate families, the only abnormalities noted were alcoholism, in one; a divorce and remarriage, in two, and a promiscuous father, in another. Socially, these students attained a fairly significant status: Two were active in the dramatic arts; one was a professional musician in a large symphony orchestra: one was a medical student, and three were advanced graduate students, one

being a member of Phi Beta Kappa. Two were teachers; another, a political radical with much publicity, and two were mediocre students with poorly defined future plans. Strikingly, none of the group had a hobby, such as woodworking, stamp collecting, or radio. In a few cases, reading and walking were listed as hobbies. Organized sports were untouched by this group, rarely even as spectators. Practically all said they spent their free time in deep discussion of art, drama, rights of man, and much common gossip, including relation of their own past histories and their reaction to its retelling. This often led to segregation of couples in more intimate discussions as bedtime approached. The likes of the group included evenings with family or friends, ballet, movies, plays, reading, dancing, and radio, especially music, and particularly the impressionistic and classical type of music of Debussy and Tschaikowsky and the nonclassical modern music of Count Basie and Duke Ellington. Most distasteful to these patients were chalk on hands, dirt, stepping on bugs, music out of tune, women in general, described as "awful," baseball, piety, required social functions, noise, police, routine, or anything approaching monotony. While opinion in the group was religiously liberal, and none expressed religious or racial prejudice, Glover felt that there is a narcissistic selfishness in their disregard for people as a whole, their lack of nationalistic or patriotic feeling, and the general disdain of inheritance and social values of law, religion, and the betterment of mankind.

Of the student patients seen by the Division of Student Hygiene at Yale University in the period reviewed for study by Fry,[3] 39% presented histories of emotional difficulty connected with sex. The incidence of sex problems among graduate students was higher than among undergraduates: More than half the graduate patients, but less than one-third of the undergraduate patients, were treated for sex difficulties. About 21% of freshmen patients who came for psychiatric help had some sex difficulty as a prominent aspect of their illness; among middle-class men the corresponding proportion was 35%; among seniors, 35%, and among graduates and professional students, 55%. About one-tenth of the students in the whole group had vague fears of homosexuality, or engaged in homosexual activity and feared becoming permanently homosexual, or were homosexual.

Fry has commented on two groups of homosexuals: (1) the active and (2) the group who have either a fear of homosexuality or an awareness of homosexual impulses. Of the first group, he says that in the college community the social habits of homosexuals attract the attention of authorities when they become disciplinary problems; that is, when they accost a student outside their own group, or when they get into drunken fights, or when they become physically or emotionally upset about love affairs. These persons are protective about their own lives but, if upset enough, will give information about others, at least in the first interview. When these fragments are put together, a description of a small group of individuals of various ages living within the community becomes available. The group is not cohesive but is composed of several knots of students, usually with one dominant person who has been around the university for some time. While the members of each clique change, the students come and go, this does not mean that the turnover is rapid. The students who make up the group may stay in the university community for many years, depending upon their career goals. Only occasionally is the activity of these homosexuals obtrusive.

The second group, those who fear homosexuality, consist primarily of boys in whom loneliness and an eager desire for friendship are commonly observed. Aggravation of his fear of homosexuality because of the greater refinement of his interests than those of the majority of his contemporaries leads the student with intellectual

or artistic ambitions to find mutual interests among homosexuals, whose attention to him is flattering. Such a boy often receives more recognition, more security, and more warmth among the homosexuals than among the rest of the community. This, in Fry's view, tends to make the students feel that their development in college, even their future careers, depends upon their relationship with a homosexual, but the intellectual bond is the only one. This group, which does not seem to be deviant in impulse, consists of a number of insecure, anxious young men whose emotional conflicts associated with homosexuality or other fantasies, appearing alone or in concert with masturbation, solitary or mutual, become forms of guilt and fear not easily shaken off. Although they seemed capable of achieving heterosexual orientation, the adjustment was often difficult. Unorganized and immature, these patients typically were physically awkward or unskilled in the kind of sport which depends more on force than on individual agility and grace. Socially insecure and seclusive, their lives were permeated with anxiety, minor obsessions, and religious conflicts. Often a disturbing relationship in the family, followed by lack of recognition and a feeling of being ignored in the college community at the outset, predisposed these boys, eager for friends but unable to find them easily, to overrespond to the kindness of anyone around them. A prey to their own confusion and to the influence of anyone who treated them kindly, these students made heroes of those offering the eagerly welcomed friendship. Unfortified by a proper knowledge of sex, they identified their sex experiences with their feelings of attachment to their heroes, became fearful of the trend of their behavior and, finally, convinced of their homosexuality. Ashamed of this possibility, afraid that it would interfere with their vocation and would deny them social recognition, they tried inconclusively to change their sex habits or to avoid the label of homosexuality. Some attempted ineffectively to find female companionship; some turned to alcohol: some to prayer; some to marriage. Some became emotionally ill. The more hysterical personalities considered suicide. Some of them finally became prominent and well-liked members of the community, often through the aid or support of homosexual friends.

Oftentimes these boys are handicapped in some way by the routine of college life: They may be older than most of their fellows or have unusual intellectual talents or interests. In some areas of life they have real or imagined inadequacies and need guidance to establish successful participation in the activities of a congenial group. The gap between these undeveloped students and their environment offers to homosexuals the chance to become the directors of their destinies, for the person who can and does enlarge their circle of friends and activities is deeply valued. This intense gratitude makes them especially susceptible to the influence of a homosexual, either a fellow student or an older person, an influence which may stimulate their intellectual or artistic interest and productivity at the same time that it directs their future careers and total development.

From 1946-1957 the primary diagnosis of homosexuality was made in 133 instances at the Student Health Service of the University of California at Los Angeles, when (1) a student stated that he was currently engaging in or had previously, since the age of 16, engaged in more than three homosexual acts or (2) had never engaged in overt homosexual activity but stated that he had prominent homosexual impulses. Like Curran, we did not include cases of "inferential or latent homosexuality" or "cases whose homosexual preference or performance seemed to be an incidental finding of secondary significance from the psychiatric point of view."

Many more than these 133 students have indicated during interviews with a Student

Health Service psychiatrist that they had engaged in an overt homosexual act at least once since the age of 16 or had prominent homosexual impulses; however, the attending psychiatrists in these cases did not, on the basis of their personal judgment, diagnose these cases as homosexual. How many are in this latter group we have no way of knowing without scrutinizing the files of every patient seen in our clinic. One hundred thirty-three is an incidence of less than 0.3% of the total number of students who have attended the University during the last 11 years. It is an incidence of about 3% of the students who visit the neuropsychiatry division of the Student Health Service, whereas in Curran's series, containing 41% who had been to a university, the incidence was about 5% of males over the age of 16 and 0.3% of females over the age of 16. In Kinsey's [4] report we read that homosexual relations are a material part of the sexual picture in single males who ultimately go to college. His figures are as follows: Between adolescence and 15 years of age, 21% are actively involved, at least in the incidental experience, to the point of orgasm; 16%, between the ages of 16 and 20; 9%, between the ages of 21 and 25, and 17%, between the ages of 26 and 30. Between adolescence and 15 years of age, about 3% of the outlet of the college male is derived from the homosexual; 2.5%, between the ages of 16 and 20; 3.7%, between the ages of 21 and 25, and 8.8%, between the ages of 26 and 30. In females, Kinsey [5] reported that the incidence of homosexual activity was correlated more definitely and truly with their educational background than was any of their other sexual activities. In single females between adolescence and 15 years of age, homosexual contact to the point of orgasm was 1% of the total outlet; between the ages of 16 and 20, 3%; between the ages of 21 and 25, 8%, and between the ages of 26 and 30, 10%.

At U. C. L. A., 75 of the 93 male homosexuals who stated their academic year were undergraduates, with a breakdown as follows: freshmen, 8; sophomores, 18; juniors, 23; seniors, 26. For both male and female homosexuals the senior year had the greatest incidence. Whereas typically 28% of the male student body is composed of graduate students, 19% of the male homosexual group was so constituted. Of a group of male nonhomosexual psychiatric patients, 16% were in graduate work. Glover's group of 12 apparently contained 4 graduate students.

Educational Status

Typically, the major fields of study distribution in the University are as follows: liberal arts and sciences, 56%; business administration, 16%; engineering, 12%; applied arts, 12%; other fields, 4%. In the group of 98 male homosexuals we found the incidence as follows: liberal arts, 48%; business administration, 11%; engineering, 4%; applied arts, 28%; other fields, 9%. Male homosexuals would seem to favor applied arts at the expense of business administration and engineering. Of the homosexuals in applied arts, 40% were in theater arts, as compared with 14% of other applied arts undergraduates.

Among Glover's 12 male patients, 2 were active in the dramatic arts, 1 was a professional musician, 1 was a medical student, and 2 were teachers. Forty-one of Curran's cases had been to universities, the most highly represented occupations being listed as follows: civil service, 7; doctors, 6; clergymen, 6; school teachers, 6; jobs connected with the stage or radio, 7.

Forty-eight (49%) of the male homosexuals in the U. C. L. A. group received undergraduate degrees, as compared with the University at large, where typically 52% of the entering male freshmen received undergraduate degrees or are in attendance eight semesters after entering. In addition, 11 of the male homosexuals in this study were still in the University at the time of this writing. Of 22 female homosexuals, 17 (77.5%) received under-

graduate degrees. In addition, 2 of the 22 were still in attendance at the time of this writing. This compares with the University at large, where typically 35% of the entering freshmen women graduate or are in attendance at the end of each semester. Of 102 male homosexuals, 28 withdrew or were dismissed by the University while on probation or making grades of less than a C average. None of the female homosexuals who left the University had poor scholastic records. In the University at large about 17% of all the students who enter typically leave the University with a below-C average.

Out of 94 male homosexuals, 17 (18%) received grades of B or better; 67 (71%) received C grades, and 10 (11%) received grade averages of less than a C for the total of their courses taken while undergraduates. This can be roughly compared with the University population at large, where the average for males is typically just slightly below midway between C and B. Of 27 female homosexuals, 10 received grade averages of B or better; 16 had C averages, and none had averages of less than C for all their undergraduate courses. The University grade average for female students is also slightly below midway between C and B.

From the grade-point averages, it appears that our male homosexual population does as well scholastically as the University population at large. However, more male homosexuals withdrew from the University with below-C averages than did University students as a whole, and the female homosexuals appeared to do better than the rest of the female students in the University.

Religion

Kinsey has commented that the highest incidences of the homosexual are among the nondevout religious group. In the upper educational levels, among religiously inactive groups, something between 10% and 50% more persons may be involved homosexually than in the actively religious groups.

Religious affiliations in Glover's group of 12 were as follows: Protestant, 7; Catholic, 2; Jewish, 2; atheist, 1. None expressed any religious taboos specifically relating to homosexuality. He felt that opinion in the group was religiously liberal and that none expressed religious prejudice. Only 2 out of the 12 attended church regularly.

Fry noted religious conflict prevalent in the group who fear homosexuality, yet are not actively deviant in impulse.

In our group, 89 of the 133 homosexuals stated these religious preferences: agnostic or atheist, 6; Buddhist, 1; Catholic, 18; Protestant, 37; Jewish, 27. The three last preferences compare with the control group at U. C. L. A. in the following manner: Among 82 homosexuals, male and female, 22% were Catholic, 45% Protestant, and 33% Jewish; in the control group, 17% were Catholic, 37% Protestant, and 46% Jewish.

Comment

Thus it would seem, from a preliminary review of data collected about these 133 homosexuals, that there were very few areas of clear-cut arithmetical difference between homosexual and nonhomosexual students. The following differences, however, do appear to exist:

1. A smaller percentage of the male homosexuals were in graduate work than was true for the rest of the University population. It was found, however, that this is also true for male psychiatric patients in general.

2. The male homosexuals tended to be in applied arts, especially theater arts, in greater percentages than the rest of the student body. Other male psychiatric patients did not show this preference for applied arts.

3. To compare the academic performance of the undergraduate homosexuals with the rest of the University undergraduate population, we compared in both groups the percentage of students leaving the University with a below-C average and the

percentage of entering freshmen eventually receiving academic degrees. Though the arithmetical averages are not identical, they are very similar, and it appears that the academic performance of the male undergraduate homosexual patients is very similar to that of their nonhomosexual peers. The academic performance of the undergraduate female homosexuals, however, appears to be decidedly better than that of other undergraduate females. Twice as many homosexual girls graduate as is typical for the University. The grade-point averages for the homosexual girls is about 0.2 higher than the average for undergraduate females.

4. A smaller percentage of male homosexuals were married than were nonhomosexual male psychiatric patients.

Treatment

That one rarely establishes a fruitful therapeutic relation with individual homosexuals is a prevalent viewpoint. In Curran's series, 25 patients treated psychotherapeutically derived no apparent benefit in terms of changed sexual preference or behavior, as compared with 25 matched patients not so treated. Fry remarks:

> Successful treatment of real sex deviates is a relatively rare achievement in the history of the college mental hygiene service. It is not always possible for the homosexual to seek the aid of anyone; and the position of the psychiatrist as part of the personnel of the university is an added barrier to therapy. The psychiatrist's primary interest is the treatment of patients, homosexual or not. But most cases of homosexuality need deep and intensive treatment which cannot be given in a university where the mental hygiene facilities must always be available to a large number of students.

According to Glover, the lassitude and inertia of homosexuals greatly contribute to the poor psychotherapeutic results. They respond to the preliminary work of preparing them for their ecologic change during the heat of remorse at being publicly exposed or legally punished, but the stigma of their pattern follows them in time, and their socialization is the most difficult thing in even the relatively enlightened atmosphere of the university. Those who have sought help without public pressure also quickly deteriorate in the strength and vigor of their efforts. In the course of the first year Glover found significant improvement in only 1 of his 12 patients.

When the homosexual comes for treatment under pressure, the results are even less satisfactory. For example, at Yale, Fry reports that about 16 established homosexuals consulted him, not of their own accord, but under pressure by the university authorities. Psychiatric contact with such patients was not at all satisfactory. If they seemed willing to accept treatment, it was only because they were obliged to do so. As a rule, they were secretive and protective about themselves, and their resistance regularly prevented the establishment of any rapport. He continues:

> The circumstances under which many homosexual cases are presented complicate the relation of patient and psychiatrist, and increases the difficulties

TABLE 1.—*Comparative Personal Data on Various Groups of Students*

	No. of Cases	Median Age, Yr.	Marital Status: Married	Single	Unknown	Religious Preference: Catholic	Protestant	Jewish	Agnostic-Atheist	Other	Unknown
Overt male homosexuals given psychotherapy	15	23.5	1	12	2	0	3	3	0	0	9
Overt male homosexuals not given psychotherapy	47	24	1	39	7	8	16	4	3	1	15
Overt male homosexuals apprehended by police—not given psychotherapy	19	25	1	17	1	4	4	5	0	0	6
All overt male homosexuals studied	81	24	3	68	10	12	23	12	3	1	30
Non-acting-out male homosexuals	28	20.5	0	23	5	3	6	10	2	0	7
All male homosexuals studied	109	23	3	91	15	15	29	22	5	1	37
Male nonhomosexuals given psychotherapy	15	22	5	9	1	1	2	3	1	1	7
Random group of male nonhomosexual psychiatric patients	62	23	13	48	1	8	19	25	10	0	0
All female homosexuals studied	24	22	0	20	4	3	8	5	1	0	7

TABLE 2.—*Comparative Academic Data Available on Various Groups of Students*

	No. of Cases	Major Field of Study						Academic Year						Grade-Point Average A=3.00 B=2.00 C=1.00
		Applied Arts	Business Administration	Engineering	Liberal Arts & Sciences	Other	Unknown	Freshman	Sophomore	Junior	Senior	Graduate	Unknown	
Overt male homosexuals given psychotherapy	15	1	1	0	11	1	1	1	0	6	3	5	0	1.83
Overt male homosexuals not given psychotherapy	47	15	4	2	19	5	2	4	11	8	11	7	6	
Overt male homosexuals apprehended by police—not given psychotherapy	19	5	2	2	6	2	2	0	1	4	7	3	4	1.56
All overt male homosexuals studied	81	21	7	4	36	8	5	5	12	18	21	15	10	1.41
Non-acting-out male homosexuals	28	6	4	0	12	0	6	3	6	5	5	3	6	1.41
All male homosexuals studied	109	27	11	4	48	8	11	8	18	23	26	18	16	1.52*
Male nonhomosexuals given psychotherapy	15	1	4	0	7	0	3	1	4	4	1	2	3	1.39
Random group of male homosexual psychiatric patients	62	5	12	19	31	5	0	8	16	11	17	10	0	
Distribution of undergraduates, fall, 1956	14,344	11.6%†	16.4%	11.9%	56.2%	4.1%								1.49
Distribution of 98 male homosexuals	98	27.6%‡	11.2%	4.1%	46.0%	8.7%								1.52
All female homosexuals studied	24	3	0	0	12	7	2	2	5	6	7	1	3	1.71§

* Those graduating or in attendance eight semesters were 58%; scholastic withdrawals or dismissals numbered 27.4%.
† Of the 11.6%; 1.7% majored in theater arts.
‡ Of the 27.6%, 11.2% majored in theater arts.
§ Those graduating or in attendance eight semesters were 86.4%; scholastic withdrawals or dismissals numbered 0.0%.

of treatment. When, for example, the psychiatrist is called in because a homosexual student is arrested for accosting people in public, the psychiatrist is not usually in a favorable position to give effective medical aid. He may, of course, be helpful in limiting the publicity given to the episode or by advising the college authorities. But in the eyes of the patient his status as physician is compromised by his connection with the authorities. In such circumstances it is usually difficult or impossible to persuade a student that the psychiatrist's interest in the problem is exclusively medical, and that information given to him will not be available to public or private administrative officials. The fact that these authorities know that the student has homosexual tendencies is enough to disturb his relation to the psychiatrist and to the rest of his environment. A similar problem arises in cases where students come to the department with the complaint that other students or older men have made homosexual advances to them. The individual consulting the psychiatrist is frequently emotionally disturbed. He may be troubled by conflicting loyalties. The psychiatrist's interest here is in the treatment of his patient, but in such a situation the psychiatrist's position is inevitably delicate since his basic responsibility as a physician to his patient is complicated by his obligations to the college authorities, to the body of students who may be influenced by the homosexuals who made advances to the patient, and to the parent of the patient. Occasionally it has been possible for the psychiatrist to discuss the problem with the homosexual with satisfactory results. But usually, however, the homosexual, feeling the psychiatrist to be a threat to his position in the community, is protective in his attitude and unwilling to talk freely about himself or the student involved.

From his experience at the University of Wisconsin, Glover reports that fear is the basic mechanism which drives patients to doctors. A homosexual, when first seen, is usually in a homosexual panic, with an intense fear of being caught, of being noticeably different, or with a fear which slowly and deeply grows to depressing proportions, that of being unable to be like other people, to be happily married, and to raise a family which will be his solace in later years. This fear of an old-age loneliness was found in all patients to be more important to them than the immediate threat of ostracism at the present time should they be discovered. Hearing of the nonjudicial psychiatric staff, these patients

TABLE 3.—*Comparative Clinical Data of Treated Groups*

	Homosexual Males Treated	Non-Acting-Out Male Homosexuals	Nonhomosexual Male Patients Treated	Homosexual Females
No. of cases	15	19	15	19
Referral source				
Self	12	11	8	14
Professor	0	2	3	2
Counseling center	0	1	2	1
Medical Dept., Student Health Service	1	0	1	1
Other and unknown	2	5	1	1
Presenting complaint				
Grades	1	0	3	1
Depression	1	1	1	4
Anxiety	3	0	3	0
Somatic	2	2	1	0
Multiple complaints	0	4	7	4
Overt homosexuality	7	0	0	9
Homosexual tendencies	0	10	0	1
Other	1	2	0	0
Reported homosexual experience				
Less than 10 homosexual acts	4	0	0	2
More than 10 homosexual acts	11	0	0	14
Reported heterosexual intercourse experience				
More than 5 times	1	1	6	5
Less than 5 times	2	2	2	3
None	6	14	6	6
No data	6	2	1	5
Reported prepubertal homosexual handling of genitals				
With children	5	1	1	6
With adults	1	0	0	1
Broken home prior to age 12	6	3	6	7
Intact home at age 12	7	14	7	10
No data	2	2	2	2
Sibling relationship				
Oldest child	1	3	3	3
Middle child	3	5	1	3
Youngest child	5	6	6	7
Only child	2	3	0	3
No data	4	2	5	3
Grade point averages	1.83	1.41	1.39	1.72

would make an appointment and in the interview would cautiously make inquiries as to the privacy of the records and the connection of the staff to any administrative or disciplinary body. The often inaccurate, frequently contradictory material provided by the patient during the first two or three interviews was corrected through several future visits; and, as the number of cases increased, the grapevine spread the news that help through the psychiatric department was available. Often the panic cases were seen as emergencies and exploded all at once in the first interview. Timing often coincided with the publication of some news item concerning homosexuality in the town, or a meeting with a girl with whom they thought a future life could be enjoyed. Both situations produced the same fear of being found wanting in normal sexual concepts and activities, and of being ostracized by society.

At U. C. L. A., with the exception of 19 cases, all the students considered in this study have come voluntarily. The relationship of the psychiatry section of the Student Health Service to the rest of the University is such that it is possible for the psychiatrist to refuse to answer even the simple question of whether or not the student has come to the Student Health Service. Under these conditions it is possible for the psychiatrist to assure the patient of the confidentiality of the doctor-patient relationship. In the event that a student is apprehended and brought to the attention of the University authorities, he is routinely referred to the psychiatric clinic of the Student Health Service. The psychiatrist who consults with him explains that in this instance his function is to report to the University authorities but that if the student wishes to consult another psychiatrist, one who is not bound to report to the University authorities, this would be available to him in the same manner that a student with any other medical illness would be free to consult a physician in the Student Health Service. When this dichotomy of function of the two psychiatrists is made clear to the student, some of the

difficulties mentioned in the Yale situation are mitigated.

While it was not felt that some revolutionary method of treatment of homosexuality would be developed out of a study, it was felt that a very considerable proportion of the students seen at the Student Health Service who were classified as homosexual could be very materially assisted and that an effort devoted in this direction would be a rewarding experience for both therapist and patient.

From the group of 133 homosexuals, 15 overt male homosexuals and 5 overt female homosexuals were given psychotherapy. This group of 20 has been compared with a nonhomosexual group of 15 male and 5 female students who have also been treated in this facility over similar periods of time. The two groups were randomly selected except for being matched for the number of hours in therapy. The 15 men in each group were roughly similar in the categories of academic year, field of study, religion, referral source, relations with people, and sibling relationships. Prepubertal homosexual or heterosexual handling of the genitals was mentioned more frequently in the charts of the male students in the homosexual group than in the charts of the other male group. As might be expected, the male patients in the control group stated they had engaged in heterosexual intercourse oftener than the homosexual male students. The median age for male students in the nonhomosexual group was 22; for the male students in the homosexual group it was 23.5. Five of the nonhomosexual male students were married; only one homosexual male student was married.

The therapists' records in all 40 of these cases were carefully reviewed. The amount of improvement as judged by the therapist was noted and classified as follows:

1. No improvement—student demonstrated no perceptible improvement
2. Mild improvement—student demonstrated in some area of his life better functioning, or increased understanding of his mode of behavior
3. Considerable improvement—clearly recognizable improvement in behavior, or a substantial decrease in intrapsychic con-

TABLE 4.—*Comparison of Therapeutic Results in Overt Homosexuals and Nonhomosexual Psychiatric Patients.**

Homosexuals				Nonhomosexuals				
Cases	No. of Sessions	Period in Psychotherapy, Mo.	Results	Cases	No. of Sessions	Period in Psychotherapy, Mo.	Results	Diagnosis
Males				Males				
1	23	10	++	1	19	4	++	Character neurosis
2	8	2	+	2	11	2	+	Psychoneurosis
3	35	14	++	3	41	13	+	Schizophrenia
4	26	8	++	4	26	9	+	Psychoneurosis
5	12 GT	6	++	5	12 GT	3	+	Anxiety reaction
6	44	20	+++	6	43	8	++	Psychoneurosis
7	46	19	++	7	45	16	+++	Anxiety reaction
8	50; 23, GT	16	++	8	72; 50 GT	28	+++	Psychoneurosis
9	30 GT	8	+	9	26 GT	9	+	Character neurosis
10	10	4	+	10	10	20	++	Character neurosis
11	38	16	++	11	40	13	+	Character neurosis
12	28	14	+++	12	35	20	++	Personal problem
13	4	5	++	13	4	4	+	Personal problem
14	64	21	+++	14	50	6	+++	Character neurosis
15	26	3	+	15	20	3	++	Character neurosis
Females				Females				
16	19	13	+++	16	22	12	++	Anxiety reaction
17	9	2	+	17	8	4	+	No diagnosis made
18	41; 40 GT	18	++	18	58; 14 GT	21	++	No diagnosis made
19	18	10	+	19	18	6	+	Character neurosis
20	35	8	++	20	24	7	+++	Psychoneurosis

Totals:

	No Improvement	Mild Improvement	Considerable Improvement
Homosexual males	4	8	3
Nonhomosexual males	7	5	3
Homosexual females	2	2	1
Nonhomosexual females	2	2	1

* GT indicates group therapy; + = no improvement; ++, mild improvement; +++, considerable improvement.

flicts as measured by psychological testing or the therapist's impression

The estimate of psychiatric improvement is always a most difficult task. By using the report of the therapists in each case as the basis for judging improvement, the same yardstick was used for judging improvement, and the same persons applied the yardstick. On this basis, as can be seen from the chart, when the therapeutic results obtained with overt male homosexuals are compared with those obtained with nonhomosexual male students, there is no meaningful difference. Hour for hour, the time spent in psychotherapy with college students presenting homosexual complaints or other psychiatric entities seems equally rewarding.

Prognostic Hints

What distinguishes these "considerably improved" patients from the other homosexuals given psychotherapy? Of the 15 overt male homosexuals, 4 had engaged in fewer than 10 homosexual acts since the age of 16. Three of those four were the ones who showed the "considerable improvement." Two of the three boys were aged 19 and 17 when first seen, considerably below the median age of 24 for 81 overt male homosexuals. We might very tentatively conclude that young age and little overt homosexual behavior are good prognostic signs for therapy with overt male homosexuals. It should be noted that only one of the four cases of "considerable improvement" demonstrated much initial motivation to change to heterosexual activity. This suggests that initial strong motivation to change from homosexual to heterosexual behavior is not always necessary for a good prognosis. Since all four of these students were better than average scholastically, high scholastic standing may be a good sign also. Those patients who showed "considerable improvement" were generally the homosexuals and nonhomosexuals who had received the greatest number of hours of therapy.

Our experience to date seems to indicate that the young, intelligent overt homosexual with little homosexual experience is apt to do well in therapy. To our surprise, the initial signs of strong motivation for change were not ordinarily present in the homosexuals benefiting from our treatment.

Conclusions

A preliminary study of data on 133 homosexuals seen in a university student health service reveals the following:

A. Homosexuals do not differ very markedly from other university students in terms of their general academic characteristics. Notable exceptions are these: 1. A smaller proportion of male homosexuals were in graduate work than was true for the rest of the university population. 2. A greater percentage of homosexual students tended to major in applied arts, especially theater arts, than in other departments. 3. The undergraduate female homosexuals turned in a decidedly better academic performance than other female undergraduates in that about twice as many homosexual girls graduate as is typical for the other girls at the university, and their grade-point averages are about 0.2 higher.

B. The non-acting-out male homosexual patients as compared with the overt homosexuals were younger, more frequently came from nonbroken homes, and engaged in less prepubertal homosexual and heterosexual handling of the genitals. Male homosexuals engaged in less heterosexual activity than their female counterparts.

C. Therapeutic experience, thus far, indicates that the results obtained by the same therapists using the same yardstick for measurement were similar and equal whether one treated psychiatric disorders of a nonhomosexual nature or of a homosexual nature. Best results obtained in the homosexual group were with the young, intelligent, overt homosexual with little homosexual experience for whom the greatest number of therapeutic hours were available. To our surprise, the initial signs of

strong motivation for change were not ordinarily present in the homosexuals benefiting from therapy. The latter observation seems worthy of further investigation.

360 N. Bedford Drive, Beverly Hills, Calif. (Dr. Ross).

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A Study of the Development of Olfactory Preferences

MARVIN STEIN, M.D.; PERRY OTTENBERG, M.D., and NORMAN ROULET, M.D., Philadelphia

The sense of smell is present at birth and plays an important role in communication between infant and mother. Independent of the mother's aid, the infant turns its head to the mother's breast at each feeding. This movement is apparently in part stimulated by the odor of the milk.[1] Odors are intimately involved in the phase of development concerned with excretory functions, and, at a later age, play a part in the genital phase of psychosexual development.

In early childhood it has been observed that all variety of objects are tasted and smelled, and usually no avertive response to odorous substances is apparent. Quite often a child may derive pleasing olfactory sensations from things which later in life, as an adult, are perceived as unpleasant. There have been many experimental investigations of adult olfactory preferences[2-4]; however, the development of these preferences has received relatively little attention. The investigation by Petó[5] is one of the few systematic attempts to study the development of olfactory attitudes.

This report will present some preliminary experimental observations and considerations on the development of olfactory preferences in apparently healthy children.

Method

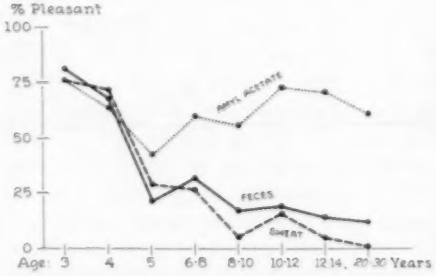
Approximately 300 healthy children between the ages of 3 and 12 years took part in this experiment. There were 25 to 60 children in each age interval, with an approximately equal number of boys and girls. The children were seen in the Pediatric Clinic of the Hospital of the University of Pennsylvania as part of their routine medical examinations. A group of adolescents was studied at one of the University of Pennsylvania Settlement Houses. In order to aid further in the study of the development of olfactory attitudes, a group of adult subjects was included.

A series of odorous substances, consisting of synthetic feces, synthetic sweat, and amyl acetate (banana-oil-like odor) were presented in a standardized manner to the subjects. The odorous substances were placed in small glass-stoppered bottles, which were wrapped in aluminum foil to minimize contamination of the outsides of the bottles with odors. With each odor the subjects were requested to close their eyes, to inhale twice, and to rate the odor as to "like" or "dislike." Adequate time was allowed between exposures to avoid interference by adaptation.

In analyzing the results, the statistical technique of χ^2 was found to be the most useful, since the data were nonquantitative.[6]

Results

A graphic representation of the development of olfactory attitudes in children can be seen in the accompanying Figure. The responses of the children are expressed as the percentage of pleasant reactions in each of the age groups. Almost all of the 3-



The development of olfactory preferences. The responses are expressed as the percentage of pleasant reactions.

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Department of Psychiatry, University of Pennsylvania School of Medicine.

Assistant Professor (Dr. Stein); Instructor (Dr. Ottenberg), Department of Psychiatry, Hospital of University of Pennsylvania.

This investigation was supported in part by a Mental Health Career Investigator Grant (M998-R) from the National Institute of Mental Health of the National Institutes of Health, U. S. Public Health Service, and a grant from the van Ameringen-Haebler Corporation, New York.

and 4-year-old children rated the odors as pleasant. It can be seen that there was a marked decrease in the "like" responses to the odors in the 5-year-old group. The decline in the percentage of pleasant reactions to feces and sweat continued into adulthood. A different response pattern is noted for amyl acetate in that following the decline in preferences at age 5 there was an increase in the percentage of pleasant reactions, which continued into adulthood.

A statistical comparison of the reactions of the children at various age intervals revealed significant differences between the responses of the 3- and 5-year-old children for feces ($P<0.001$), sweat ($P<0.001$), and amyl acetate ($P<0.02$). After the age of 5 years there were no further significant decreases in the number of pleasant judgments of feces or sweat. There was a significant difference ($P<0.01$) between the responses to amyl acetate of the 5- and the 10-12-year age groups, which was not found with feces. A comparison of the responses to amyl acetate with those to feces and sweat at each of the age intervals revealed that after the age of 5 the reactions were significantly different ($P<0.001$). This difference was not found between the reactions to feces and to sweat.

There were no significant differences between sexes in the responses to any of the odors.

Comment

At birth the infant is biologically endowed with unlearned, inherited responses to olfactory stimuli. These earliest reactions to odors are responses to be categorized primarily as approach or avoidance. An example of approach in newborn infants is the sucking response, which Jensen [1] found is released by olfactory stimuli. Avoidance responses to odors in the newborn have been demonstrated by Kussmaul,[5] who found that sleeping newborn babies became restless and cried loudly when exposed to the odor of asafetida. Preyer and Kroner [5] tested the newborn's reactions by coating the nipples of nursing mothers with odorous substances and observed violent avoidance reactions.

As suggested by Ostow,[7] the early reflex responses to odors have a strong affective component of pleasantness or unpleasantness. Some of these initial affective responses to odors are modified through experience. The most readily observable changes in the evaluation of odors are in the direction of dislike. Often a child may derive pleasing olfactory sensations from odors which to the adult are unpleasant. From the findings of this report, as well as clinical observations, the dislike of the odor of feces and sweat is an example of such acquired affective responses. The majority of the 3-year-old children found the odor of feces or sweat to be pleasant, in marked contrast to the ratings found for the adult population.

Such reversals of olfactory affective judgments have been related to early childhood experiences and to the mastery of instinctual impulses. Although olfactory experiences have been considered important in the oral stage of psychosexual development, the modification of olfactory preferences is frequently related to the anal phase. Ferenczi,[8] Berg,[9] and others,[10] have stressed the particular role of reaction formation in the anal stage in the development of olfactory preferences.

Of interest is the observation in this report that the significant change in olfactory reactions to feces and sweat occurs at the age of 5 to 6, rather than during the earlier period of toilet training (Figure). These changes, therefore, may be related to the panrepression of erotic drives that is initiated by the Oedipal conflict. It has been suggested that repression alone is not always sufficient for the resolution of the Oedipus complex.[11] There may also be a temporary regression to pregenitality, with the development of reaction formations as defenses against the pregenital impulses. The reversal in olfactory preference for the

odors of feces and sweat may be such a reaction formation.

The significant change in olfactory preferences at the age of 5 to 6 was not limited, however, to the odors of feces and sweat. The children's reactions to amyl acetate also showed a significant decrease in pleasant responses at this time. After the age of 5 the response pattern to amyl acetate was quite different, however, from that to feces, with a significant difference beginning at the age of 6. This increase in "like" responses to amyl acetate after the age of 5 may be an example of sublimation, with diversion from sexual to nonsexual aims, since during latency the odor reminded boys of model airplane "dope" and girls of fingernail polish remover. The role of sublimation in the development of the child during the latency period has been noted by others.[11]

The data reported herein suggest that although adult olfactory preferences may have their roots in pregenitality, the significant changes in olfactory preferences first appear during the Oedipal phase, then become consolidated, and persist during the latency period.

Summary

A series of odorous substances consisting of synthetic feces, synthetic sweat, and amyl acetate were presented to a group of 300 children between the ages of 3 and 12 years. With each odor the subjects were requested to rate the odor as to whether they liked or disliked it. Almost all of the 3- and 4-year-old children rated the odors as pleasant. There was a significant decrease at the age of 5 in the percentage of pleasant reactions to the odors. The findings are discussed in relation to psychosexual development.

Dept. of Psychiatry, Hospital of University of Pennsylvania.

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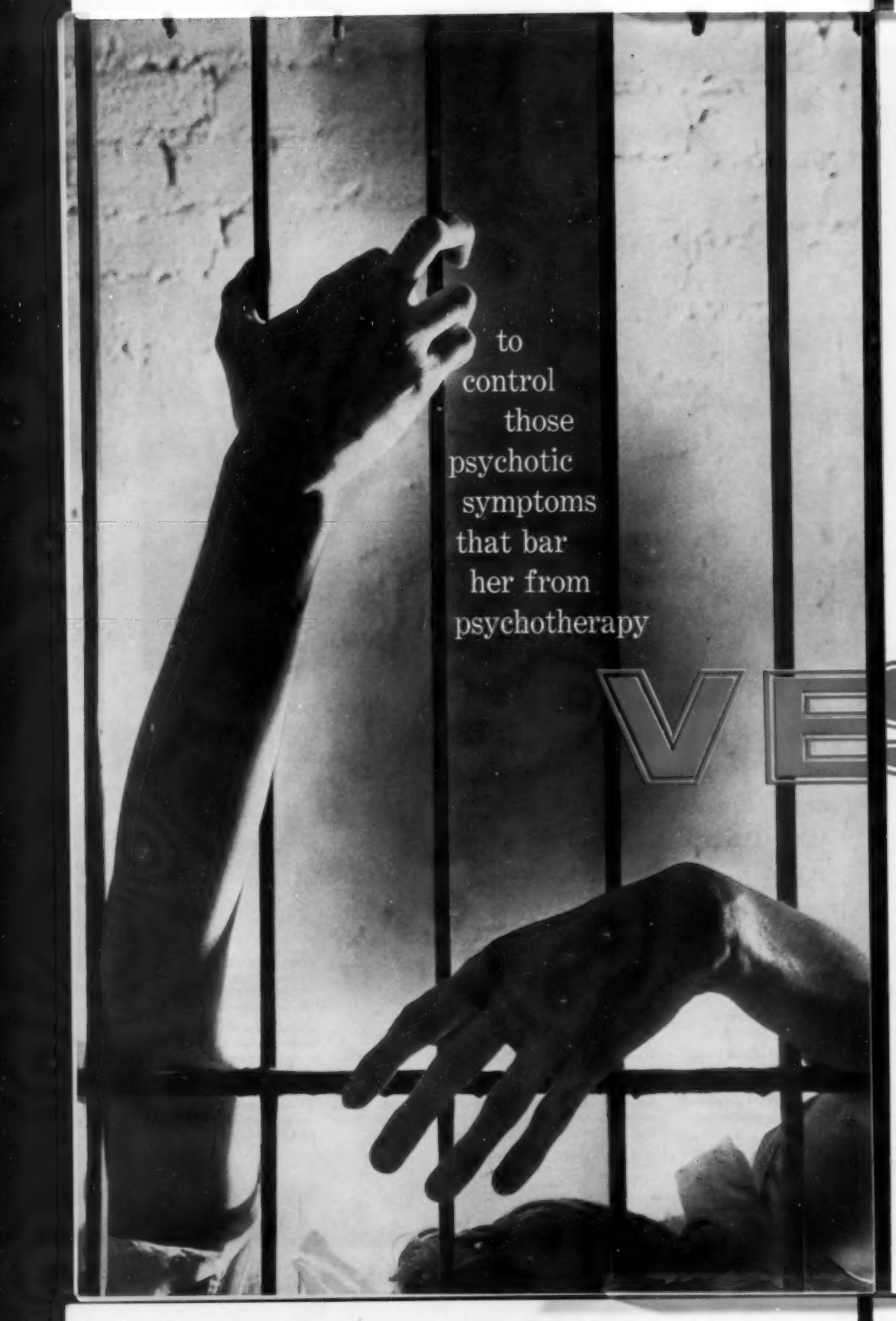
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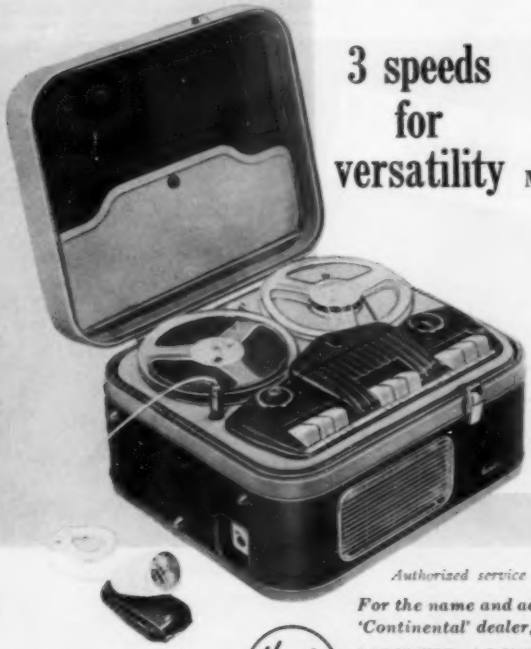

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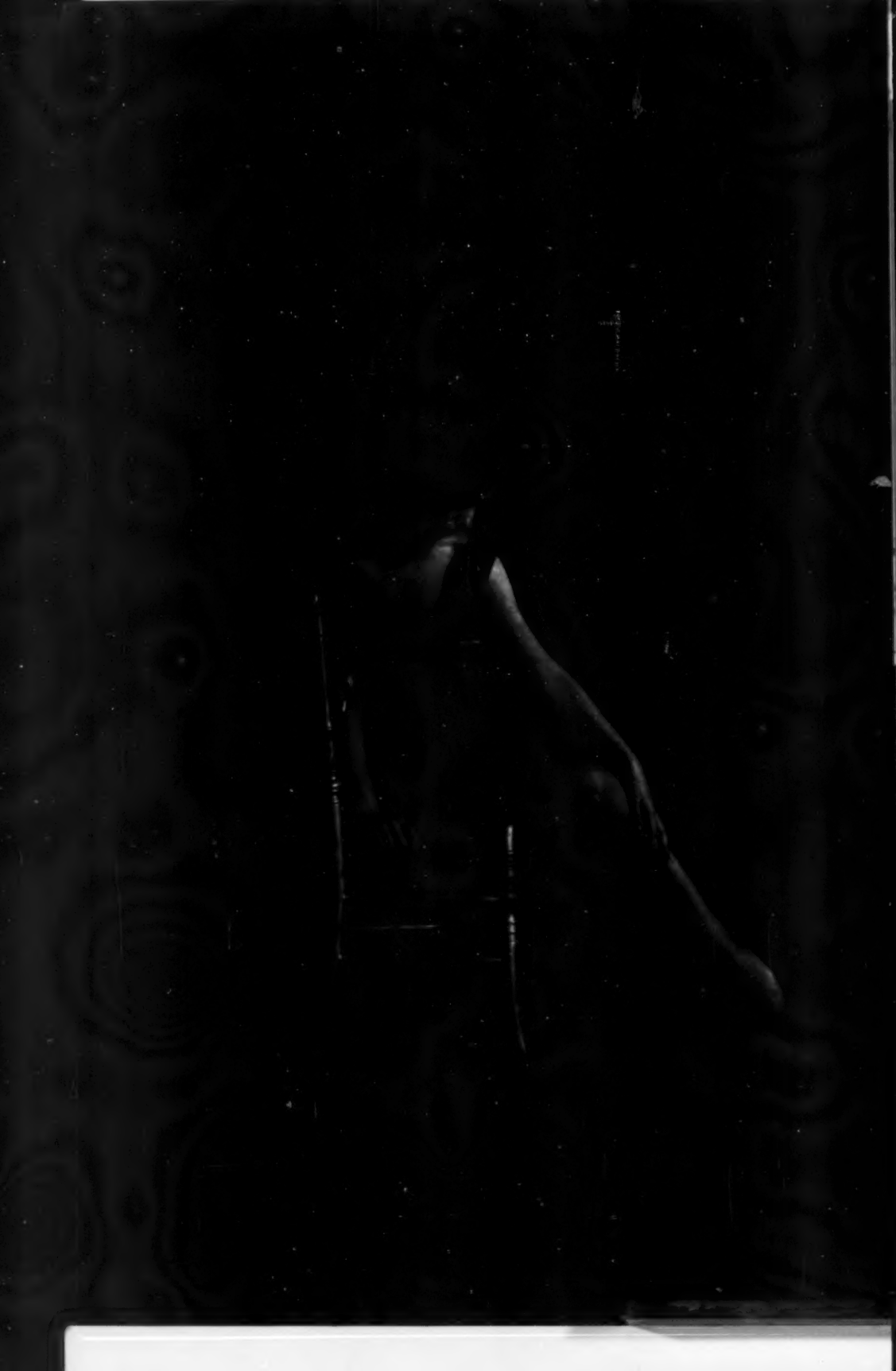

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